



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 211/06, 213/02, 215/02, 239/02, 309/02, A61K 31/35, 31/44, 31/445, 31/47, 31/505		A1	(11) International Publication Number: WO 98/47869 (43) International Publication Date: 29 October 1998 (29.10.98)
(21) International Application Number: PCT/US98/08004 (22) International Filing Date: 22 April 1998 (22.04.98)		(74) Agents: ESMOND, Robert, W. et al.; Sterne, Kessler, Goldstein & Fox P.L.L.C., Suite 600, 1100 New York Avenue, N.W., Washington, DC 20005-3934 (US).	
(30) Priority Data: 60/044,530 22 April 1997 (22.04.97) US 60/062,649 22 October 1997 (22.10.97) US		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(71) Applicant (for all designated States except US): CoCENSYS, INC. [US/US]; 201 Technology Drive, Irvine, CA 92618 (US).		Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(72) Inventors; and (75) Inventors/Applicants (for US only): WANG, Yan [CN/US]; 25 Bearpaw #27C, Irvine, CA 92604 (US). CAI, Sui, Xiong [CN/US]; 12 Salinas, Foothill Ranch, CA 92610 (US). LAN, Nancy, C. [US/US]; 522 Hermosa Street, Pasadena, CA 91030 (US). KEANA, John, F., W. [US/US]; 3854 Onyx Street, Eugene, OR 97405 (US). ILYIN, Victor, I. [RU/US]; 5205 Paloverde Road, Irvine, CA 92612-4305 (US). WEBER, Eckard [US/US]; 1290 Morningside, Laguna Beach, CA 92651 (US).			
(54) Title: CARBOCYCLIC AND HETEROCYCLIC SUBSTITUTED SEMICARBAZONES AND THIOSEMICARBAZONES AND THE USE THEREOF			
(57) Abstract			
<p>This invention is related to carbocyclic and heterocyclic substituted semicarbazones and thiosemicarbazones represented by formula (I), or a pharmaceutically acceptable salt or prodrug thereof, wherein: Y is oxygen or sulfur; R₁, R₂₁, R₂₂ and R₂₃ are independently hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl; or R₂₂ and R₂₃, together with the N, form a heterocycle; A₁ and A₂ are independently aryl, heteroaryl, saturated or partially unsaturated carbocycle or saturated or partially unsaturated heterocycle, any of which is optionally substituted; X is one or O, S, NR₂₄, CR₂₅R₂₆, C(O), NR₂₄CO, C(O)NR₂₄, SO, SO₂ or a covalent bond; where R₂₄, R₂₅ and R₂₆ are independently hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl. The invention is also directed to the use of carbocycle and heterocycle substituted semicarbazones and thiosemicarbazones for the treatment of neuronal damage following global and focal ischemia, for the treatment or prevention of neurodegenerative conditions such as amyotrophic lateral sclerosis (ALS), for the treatment and prevention of otoneurotoxicity and eye diseases involving glutamate toxicity and for the treatment, prevention or amelioration of pain, as anticonvulsants, and as antimanic depressants, as local anesthetics, as antiarrhythmics and for the treatment or prevention of diabetic neuropathy and urinary incontinence.</p>			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

Carbocyclic and Heterocyclic Substituted Semicarbazones and Thiosemicarbazones and the Use Thereof

Background of the Invention

5

Field of the Invention

10 This invention is in the field of medicinal chemistry. In particular, the invention relates to carbocyclic and heterocyclic substituted semicarbazones and thiosemicarbazones, and the discovery that these compounds act as blockers of sodium (Na^+) channels.

Related Art

15 Several classes of therapeutically useful drugs, including local anesthetics such as lidocaine and bupivacaine, antiarrhythmics such as propafenone and amioclарone, and anticonvulsants such as lamotrigine, phenytoin and carbamazepine, have been shown to share a common mechanism of action by blocking or modulating Na^+ channel activity
20 (Catterall, W.A., *Trends Pharmacol. Sci.* 8:57-65 (1987)). Each of these agents is believed to act by interfering with the rapid influx of Na^+ ions.

25 Recently, other Na^+ channel blockers such as BW619C89 and lifarizine have been shown to be neuroprotective in animal models of global and focal ischemia and are presently in clinical trials (Graham *et al.*, *J. Pharmacol. Exp. Ther.* 269:854-859 (1994); Brown *et al.*, *British J. Pharmacol.* 115:1425-1432 (1995); *SCRIP* 1870:8 (1993); *SCRIP* 1773:14 (1992)).

30 The neuroprotective activity of Na^+ channel blockers is due to their effectiveness in decreasing extracellular glutamate concentration during ischemia by inhibiting the release of this excitotoxic amino acid neurotransmitter. Studies have shown that unlike glutamate receptor antagonists, Na^+ channel blockers prevent hypoxic damage to mammalian white matter (Stys *et al.*, *J. Neurosci.* 12:430-439 (1992)). Thus, they may offer advantages for treating certain types of strokes or neuronal trauma where damage to white matter tracts is prominent. In addition to playing a major role
35 in neurotoxicity involving stroke, glutamate is also a key neurotransmitter which mediates otoneurotoxicity resulting in acute or progressive hearing loss and tinnitus (Pujol *et al.* *Acta Otolaryngol (Stockh)* 113:330-334 (1993)).

- 2 -

Therefore, Na^+ channel blockers are expected to be effective in preventing and treating otoneurotoxicity by decreasing extracellular glutamate concentration. Similarly, Na^+ channel blockers will be useful for preventing and treating eye diseases involving excitatory toxicity such as glaucoma and CMV retinitis.

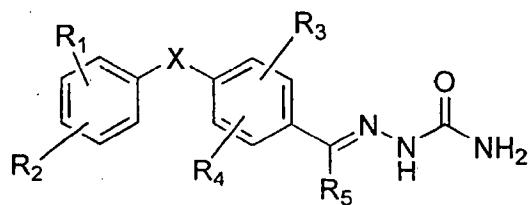
5 Another example of clinical use of a Na^+ channel blocker is riluzole. This drug has been shown to prolong survival in a subset of patients with ALS (Bensimmo *et al.*, *New Engl. J. Med.* 330:585-591 (1994)) and has subsequently been approved by the FDA for the treatment of ALS. In addition to the above-mentioned clinical uses, carbamazepine, lidocaine and phenytoin 10 are occasionally used to treat neuropathic pain, such as from trigeminal neurologia, diabetic neuropathy and other forms of nerve damage (Taylor and Meldrum, *Trends Pharmacol. Sci.* 16:309-316 (1995)), and carbamazepine and lamotrigine have been used for the treatment of manic depression (Denicott *et al.*, *J. Clin. Psychiatry* 55: 70-76 (1994)).

15 It has been established that there are at least five to six sites on the voltage-sensitive Na^+ channels which bind neurotoxins specifically (Catterall, W.A., *Science* 242:50-61 (1988)). Studies have further revealed that therapeutic antiarrhythmics, anticonvulsants and local anesthetics whose actions are mediated by Na^+ channels, exert their action by interacting with 20 the intracellular side of the Na^+ channel and allosterically inhibiting interaction with neurotoxin receptor site 2 (Catterall, W.A., *Ann. Rev. Pharmacol. Toxicol.* 10:15-43 (1980)).

25 PCT International Published Application WO94/06758 discloses a genus of aryl semicarbazones that have anticonvulsant activity in the maximal electroshock screen when orally administered to rats.

Dimmock *et al.*, *J. Med. Chem.* 36:2243-2252 (1993) discloses aryl semicarbazones and aryl thiosemicarbazones that display oral activity as anticonvulsants in rats.

30 PCT International Published Application WO96/40628 discloses semicarbazones represented by Formula IX:



IX

where R_1 - R_4 are independently hydrogen, halogen, C_{1-9} alkyl, C_{3-9} cycloalkyl, cyano, C_{1-9} alkoxy, or C_{6-10} aryloxy; R_5 is hydrogen, C_{1-9} alkyl, C_{3-9} cycloalkyl, or C_{6-10} aryl; and X is oxygen or sulfur. The compounds are disclosed to be useful as anticonvulsants.

5 Dimmock *et al.*, *J. Med. Chem.* 39:3984-3997 (1996) discloses (aryloxy)aryl semicarbazones that displayed anticonvulsant activities when administered intraperitoneally to mice or orally to rats.

10 The compounds that are disclosed in each of the aforementioned documents are described as having anticonvulsant activities. However, their mechanism of action had not been elucidated.

Summary of the Invention

15 The present invention is related to treating a disorder responsive to the blockade of sodium channels in a mammal suffering from excess activity of said channels by administering an effective amount of a compound of Formula I or Formula IX as described herein. The present invention is also related to treating a disorder responsive to the blockade of sodium channels in a mammal suffering therefrom by administering an effective amount of a compound of 20 Formula VI as described herein.

25 The present invention is also directed to the use of a compound of Formulae I, VI or IX for the treatment of neuronal damage following global and focal ischemia, for the treatment or prevention of otoneurotoxicity, for the treatment and prevention of eye diseases involving excitatory toxicity, and for the treatment or prevention of neurodegenerative conditions such as amyotrophic lateral sclerosis (ALS), as antimanic depressants, as local anesthetics, as antiarrhythmics and for the treatment or prevention of diabetic neuropathy and for the treatment of pain including chronic pain. The compounds may also be useful for urinary incontinence.

30 The present invention also is directed to the process for preparing novel substituted semicarbazones and thiosemicarbazones of Formulae I or IX.

- 4 -

A first aspect of the present invention is directed to the use of compounds of Formulae I, VI or IX as blockers of sodium channels.

5 A second aspect of the present invention is to provide a method for treating, preventing or ameliorating neuronal loss following global and focal ischemia; treating, preventing or ameliorating pain including chronic pain; treating, preventing or ameliorating neurodegenerative conditions, otoneurotoxicity and eye diseases involving glutamate toxicity; treating, preventing or ameliorating manic depression; inducing local anesthesia; and treating arrhythmias by administering a compound of Formulae I, VI or IX to 10 a mammal in need of such treatment.

A number of compounds within the scope of the present invention are novel compounds. Therefore, a third aspect of the present invention is to provide novel compounds of Formulae I or IX, and to also provide for the use of these novel compounds for treating, preventing or ameliorating convulsions.

15 A fourth aspect of the present invention is to provide a pharmaceutical composition useful for treating disorders responsive to the blockade of sodium ion channels, containing an effective amount of a compound of Formulae I, VI or IX in admixture with one or more pharmaceutically acceptable carriers or diluents.

20 A fifth aspect of the present invention is directed to methods for preparing novel compounds of Formulae I or IX.

Brief Description of the Drawings

25 FIGS. 1A, 1B, 1C and 1D are graphs of the antinociceptive effects (time licking) of a compound of the present invention as a function of oral (not shaded) or i.p. (shaded) doses of said compound. The effects were measured in the formalin test in mice as described herein.

Detailed Description of the Invention

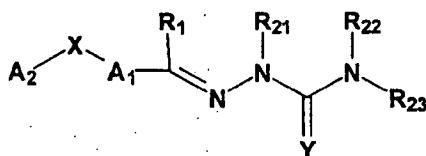
30 The present invention arises out of the discovery that compounds of Formulae I, VI and IX act as blockers of the Na^+ channel. In view of this

- 5 -

discovery, compounds of Formulae I and IX are useful for treating disorders responsive to the blockade of sodium ion channels.

The compounds useful in this aspect of the present invention are semicarbazones and thiosemicarbazones represented by Formula I:

5



I

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

Y is oxygen or sulfur;

10 R₁ is hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl;

R₂₁, R₂₂ and R₂₃ are independently hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl, or R₂₁ is defined as above, and R₂₂ and R₂₃ together with the nitrogen atom to which they are attached form a heterocycle, including piperidine, piperazine, or morpholine;

15 A₁ and A₂ are independently aryl, heteroaryl, saturated or partially unsaturated carbocycle or saturated or partially unsaturated heterocycle, any of which is optionally substituted;

20 X is one or O, S, NR₂₄, CR₂₅R₂₆, C(O), NR₂₄C(O), C(O)NR₂₄, SO, SO₂ or a covalent bond; where

R₂₄ is hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl; and

25 R₂₅ and R₂₆ are independently hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl.

Preferred compounds falling within the scope of Formula I include compounds wherein A₁ and A₂ are both aryl moieties, preferably both phenyl moieties, that are each optionally independently substituted by one or two substituents independently selected from the group consisting of halogen, nitro, amino, C₁₋₆ alkyl, C₃₋₈ cycloalkyl, cyano, C₁₋₆ alkoxy or C₆₋₁₀ aryloxy; Y is O; R₁ is hydrogen, C₁₋₆ alkyl, C₃₋₈ cycloalkyl or C₆₋₁₀ aryl; R₂₁, R₂₂ and R₂₃ are independently hydrogen or C₁₋₆ alkyl; and X is oxygen or sulfur.

Preferred compounds within Formula I also include those compounds where A_1 is an optionally substituted aryl group selected from the group consisting of phenyl and naphthyl, and A_2 is an optionally substituted heteroaryl or aryl group selected from the group consisting of pyridyl, pyrimidinyl, 1,3,5-triazinyl, furanyl, thiophenyl, naphthyl, quinolyl, 3,4-methylenedioxophenyl, 3,4-ethylenedioxophenyl, indanyl, tetrahydronaphthyl and quinoxalinyl.

Additional preferred compounds within Formula I also include those compounds where A_1 is an optionally substituted aryl group selected from the group consisting of phenyl or naphthyl, and A_2 is an optionally substituted carbocycle or heterocycle selected from the group consisting of cyclopentyl, cyclohexyl, cycloheptyl, piperidinyl, morpholinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydropyranyl, cyclohexenyl, adamantyl, *exo*-norbornyl and cyclopentenyl.

Additional preferred compounds within Formula I include those compounds where A_1 is an optionally substituted heteroaryl or aryl group selected from the group consisting of pyridyl, pyrimidinyl, 1,3,5-triazinyl, naphthyl, quinolyl, furanyl, and thiophenyl, and A_2 is an optionally substituted heteroaryl or aryl group selected from the group consisting of phenyl, furanyl, thiophenyl, quinolinyl, 3,4-methylenedioxophenyl, 3,4-ethylenedioxophenyl, indanyl, tetrahydronaphthyl and naphthyl.

Additional preferred compounds within Formula I include those compounds where A_1 is an optionally substituted, saturated or partially unsaturated carbocycle or heterocycle selected from the group consisting of cyclopentyl, cyclohexyl, cycloheptyl, morpholinyl, piperidinyl, pyrrolidinyl, tetrahydrofuranyl and tetrahydropyranyl, and A_2 is an optionally substituted aryl or heteroaryl group selected from the group consisting of phenyl, furanyl, thiophenyl, quinolinyl, 3,4-methylenedioxophenyl, 3,4-ethylenedioxophenyl, indanyl, tetrahydronaphthyl, or naphthyl.

Exemplary preferred compounds that may be employed in this method of invention include, without limitation:

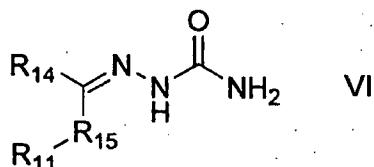
4-phenoxybenzaldehyde semicarbazone;
4-(4-fluorophenoxy)benzaldehyde semicarbazone;
4-(4-chlorophenoxy)benzaldehyde semicarbazone;
4-(4-bromophenoxy)benzaldehyde semicarbazone;
4-(4-methoxyphenoxy)benzaldehyde semicarbazone;

4-(4-trifluoromethylphenoxy)benzaldehyde semicarbazone;
4-(4-methylphenoxy)benzaldehyde semicarbazone;
4-(3,4-difluorophenoxy)benzaldehyde semicarbazone;
4-(4-chloro-2-fluorophenoxy)benzaldehyde semicarbazone;
5 4-(4-nitrophenoxy)benzaldehyde semicarbazone;
4-(3-methylphenoxy)benzaldehyde semicarbazone;
4-(4-t-butylphenoxy)benzaldehyde semicarbazone;
4-(4-propylphenoxy)benzaldehyde semicarbazone;
4-(4-s-butylphenoxy)benzaldehyde semicarbazone;
10 4-(4-bromophenoxy)acetophenone semicarbazone;
4-(4-fluorophenoxy)acetophenone semicarbazone;
4-(4-chlorophenoxy)acetophenone semicarbazone;
4-(4-bromophenoxy)propiophenone semicarbazone;
4-(4-fluorophenoxy)propiophenone semicarbazone;
15 4-(4-chlorophenoxy)propiophenone semicarbazone;
4-(2-pyridinoxy)benzaldehyde semicarbazone;
4-(3-pyridinoxy)benzaldehyde semicarbazone;
4-(4-pyridinoxy)benzaldehyde semicarbazone;
4-(2-pyrimidinoxy)benzaldehyde semicarbazone;
20 4-(4-chloro-2-pyridinoxy)benzaldehyde semicarbazone;
2-phenoxy pyridine-5-carboxaldehyde semicarbazone;
2-(4-chlorophenoxy)pyridine-5-carboxaldehyde semicarbazone;
2-(4-fluorophenoxy)pyridine-5-carboxaldehyde semicarbazone;
4-(3,4-methylenedioxyphenoxy)benzaldehyde semicarbazone;
25 4-phenyl mercaptobenzaldehyde semicarbazone;
4-(4-fluorophenylmercapto)benzaldehyde semicarbazone;
4-(4-chlorophenylmercapto)benzaldehyde semicarbazone;
4-cyclohexyloxybenzaldehyde semicarbazone;
4-cycloheptyloxybenzaldehyde semicarbazone;
30 4-(5-indanyloxy)benzaldehyde semicarbazone;
4-(6-quinolinylloxy)benzaldehyde semicarbazone;
4-(4-fluorophenoxy)-3-fluorobenzaldehyde semicarbazone;
4-(4-fluorophenoxy)cyclohexane-1-carboxaldehyde semicarbazone;
4-(tetrahydropyranloxy)benzaldehyde semicarbazone;
35 4-(1-methyl-4-piperidinoxy)benzaldehyde semicarbazone;
4-(4-fluorophenoxy)benzaldehyde 4'-methylsemicarbazone; and

- 8 -

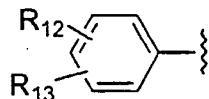
4-(4-fluorophenoxy)benzaldehyde 2'-methylsemicarbazone.

Additionally, compounds of Formula VI can also be employed to block sodium (Na⁺) channels:



or a pharmaceutically effective salt thereof; wherein

R₁₁ is



15 or R₁₁ is a 5 to 7 member heterocycle having between 1 and 3 heteroatoms selected from the group consisting of O, S and N, said heterocycle being unsubstituted or substituted with at least one substituent selected from the group consisting of halogen, amino, lower alkylamino, dilower alkylamino, lower alkoxy and aryl, wherein said aryl is unsubstituted or substituted with at least one substituent selected from the group consisting of halogen, amino, lower alkylamino, dilower alkylamino and lower alkoxy;

20 R₁₂ and R₁₃ are the same or different and are selected from hydrogen, halogen, lower alkyl, amino, nitro, lower alkoxy, lower alkylidene and lower arylidene, said lower alkyl being unsubstituted or substituted with at least one substituent selected from the group consisting of halogen, amino, lower alkylamino, dilower alkylamino and aryl, wherein said aryl is unsubstituted or substituted with at least one substituent selected from the group consisting of hydrogen, halogen, lower alkyl, lower alkoxy, amino, lower alkylamino and dilower alkylamino, said lower alkoxy, lower alkylidene and lower arylidene being unsubstituted or substituted with at least one substituent selected from the group consisting of halogen, amino, lower alkylamino, dilower alkylamino, lower alkoxy and aryl, wherein said aryl is unsubstituted or substituted with at least one substituent selected from the group consisting of halogen, amino, lower alkylamino, dilower alkylamino and lower alkoxy;

25

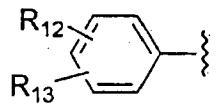
30

R_{14} is hydrogen, alkyl, alkylidene, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl; and

R_{15} is a single bond, an alkyl having between 1 and 10 carbon atoms or an alkylidene having between 2 and 20 carbon atoms, said alkyl being unsubstituted or substituted with at least one substituent selected from the group consisting of halogen, amino, lower alkylamino, dilower alkylamino, lower alkoxy and aryl, wherein said aryl is unsubstituted or substituted with at least one substituent selected from the group consisting of halogen, amino, lower alkylamino, dilower alkylamino and lower alkoxy, said alkylidene being unsubstituted or substituted with at least one substituent selected from the group consisting of halogen, amino, lower alkylamino, dilower alkylamino and aryl, wherein said aryl is unsubstituted or substituted with at least one substituent selected from the group consisting of hydrogen, halogen, lower alkyl, lower alkoxy, amino, lower alkylamino and dilower alkylamino.

Preferred compounds within the scope of Formula VI include those compounds where:

R_{11} is



R_{12} and R_{13} are the same or different and are selected from hydrogen, fluorine, chlorine, bromine, iodine, lower alkoxy and lower alkyl;

R_{14} is hydrogen; and

R_{15} is a single bond, lower alkyl or a substituted or unsubstituted alkylidene having between 2 and 20 carbon atoms.

Since the compounds of Formula I and VI are blockers of sodium (Na^+) channels, a number of diseases and conditions mediated by sodium ion influx can be treated employing these compounds. Therefore, the invention is related to a method of treating, preventing or ameliorating neuronal loss associated with stroke, global and focal ischemia, CNS trauma, hypoglycemia and surgery, spinal cord trauma; as well as treating or ameliorating neurodegenerative diseases including Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease, treating or ameliorating anxiety, convulsions, glaucoma, migraine headache, and muscle spasm. The compounds of Formula

- 10 -

I and VI are also useful as antimanic depressants, as local anesthetics, and as antiarrhythmics; as well as for treating, preventing or ameliorating pain including surgical, chronic and neuropathic pain. In each instance, the methods of the present invention require administering to an animal in need of such treatment an effective amount of a sodium channel blocker of the present invention, or a pharmaceutically acceptable salt or prodrug thereof.

5 The present invention is also directed to novel compounds within the scope of Formula I. These compounds include those compounds of Formula I where:

10 Y is oxygen or sulfur;

R₁ is hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl;

15 R₂₁, R₂₂ and R₂₃ are independently hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl, or R₂₁, is defined as above, and R₂₂ and R₂₃ together with the nitrogen atom to which they are attached form a heterocycle, including piperidine, piperazine, morpholine;

20 A₁ and A₂ are independently aryl, heteroaryl, saturated or partially unsaturated carbocycle or saturated or partially unsaturated heterocycle, any of which is optionally substituted;

X is one or O, S, NR₂₄, CR₂₅R₂₆, C(O), NR₂₄C(O), C(O)NR₂₄, SO, SO₂ or a covalent bond; where

25 R₂₄ is hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl; and

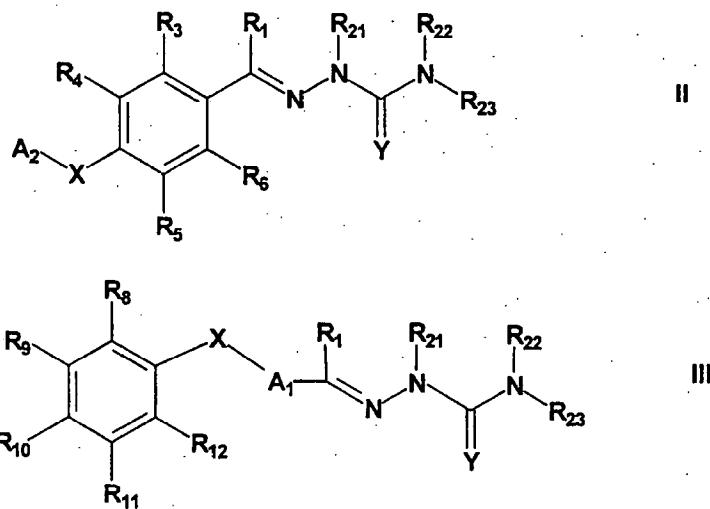
R₂₅ and R₂₆ are independently hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl;

provided that:

30 when X is O or S, R₂₁, R₂₂ and R₂₃ are hydrogen or alkyl, then A₁ and A₂ are not both phenyl, optionally substituted by one or two non-hydrogen substituents.

Specifically, preferred substituted semicarbazones and thiosemicarbazones are represented by Formulae II-VI and VIII-IX. In particular, a preferred embodiment is represented by Formulae II and III:

- 11 -



or a pharmaceutically acceptable salt or prodrug thereof, wherein R₁,
 5 R₂₁, R₂₂, R₂₃, X, Y, A₁ and A₂ are as defined previously with respect to
 Formula I, provided that A₁ and A₂ are other than optionally substituted
 phenyl; and

10 R₃, R₄, R₅ and R₆ independently are hydrogen, halo, haloalkyl, aryl,
 cycloalkyl, saturated or partially unsaturated heterocycle, heteroaryl, alkyl,
 alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl,
 hetroarylalkenyl, heteroarylalkynyl, cycloalkylalkyl, heterocycloalkyl,
 hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxyalkyl, nitro, amino, ureido,
 cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy,
 carbonylamido or alkylthiol; or

15 R₃ and R₄ or R₅ and R₆ are taken together with the carbon atoms to
 which they are attached to form a carbocycle or heterocycle. Examples of
 bridges formed by R₃ and R₄ or R₅ and R₆ taken together are —OCH₂O—,
 —OCF₂O—, —(CH₂)₃—, —(CH₂)₄—, —OCH₂CH₂O—,
 —CH₂N(R₇)CH₂—, —CH₂CH₂N(R₇)CH₂—, —CH₂N(R₇)CH₂CH₂— and
 20 —CH=CH—CH=CH—; where R₇ is hydrogen, alkyl or cycloalkyl;

25 R₈, R₉, R₁₀, R₁₁ and R₁₂ independently are hydrogen, halo, haloalkyl,
 aryl, cycloalkyl, saturated or partially unsaturated heterocycle, heteroaryl,
 alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl,
 hetroarylalkenyl, heteroarylalkynyl, cycloalkylalkyl, heterocycloalkyl,
 hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxyalkyl, nitro, amino, ureido,

- 12 -

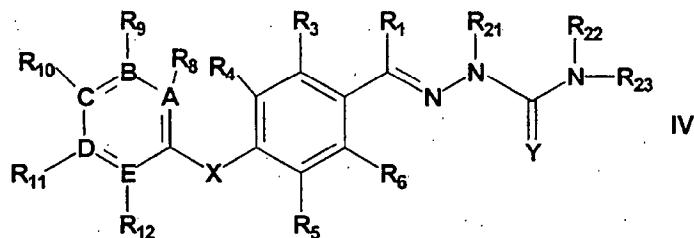
cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido or alkylthiol; or

one of R₈ and R₉, or R₉ and R₁₀, or R₁₀ and R₁₁, or R₁₁ and R₁₂ are taken together with the carbon atoms to which they are attached to form a carbocycle or heterocycle. Examples of bridges formed by R₈ and R₉, or R₉ and R₁₀, or R₁₀ and R₁₁, or R₁₁ and R₁₂ taken together are —OCH₂O—, —OCF₂O—, —(CH₂)₃—, —(CH₂)₄—, —OCH₂CH₂O—, —CH₂N(R₇)CH₂—, —CH₂CH₂N(R₇)CH₂—, —CH₂N(R₇)CH₂CH₂— and —CH=CH—CH=CH—; where R₇ is hydrogen, alkyl or cycloalkyl.

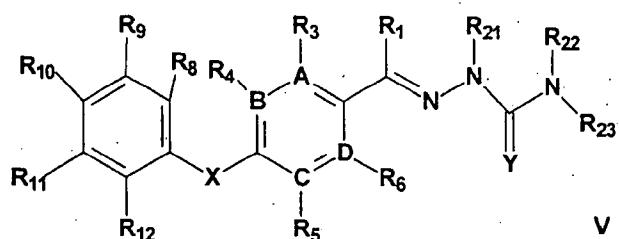
Preferred values of A₂ in Formula II include furanyl, thiophenyl, quinolinyl, 3,4-methylenedioxophenyl, 3,4-ethylenedioxophenyl, indanyl, tetrahydronaphthyl, and naphthyl.

Preferred values of A₁ in Formula III include furanyl, thiophenyl, quinolinyl, 3,4-methylenedioxophenyl, 3,4-ethylenedioxophenyl, indanyl, tetrahydronaphthyl and naphthyl.

Another preferred embodiment of the invention includes substituted semicarbazones and thiosemicarbazones represented by Formula IV and Formula V:



20



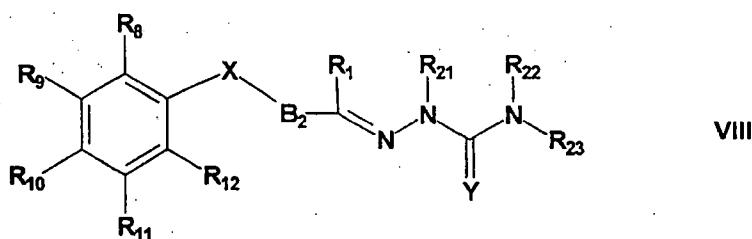
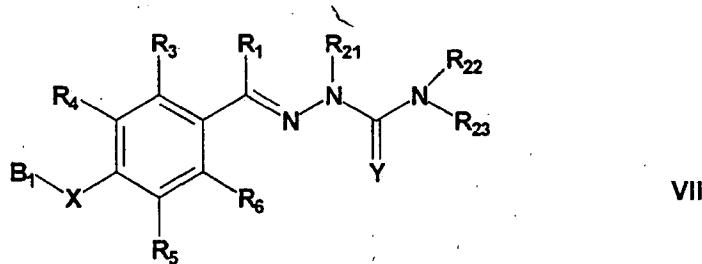
25 or a pharmaceutically acceptable salt or prodrug thereof, wherein

R₁, R₃-R₆, R₈-R₁₂, Y and X are as defined previously with respect to Formulae I, II and III; and

5 A, B, C, D and E are independently nitrogen or carbon, provided that no more than three of A, B, C, D and E are nitrogen, and there is no substituent, except for oxygen (when the nitrogen is present as a N-oxide), present on A, B, C, D or E when said A, B, C, D or E represents nitrogen.

Preferred compounds of Formula IV are those where one, two or three of A through E are nitrogens. Preferred compounds of Formula V are those where one or two of A through D are nitrogens.

10 Another preferred embodiment of the invention includes substituted semicarbazones and thiosemicarbazones represented by Formula VII and Formula VIII:



15 or a pharmaceutically acceptable salt or prodrug thereof, wherein

R₁, R₃-R₆, R₈-R₁₂, Y and X are as defined previously with respect to Formula I through III;

20 B₁ is an optionally substituted, saturated or partially unsaturated carbocycle or optionally substituted, saturated or partially unsaturated heterocycle; and

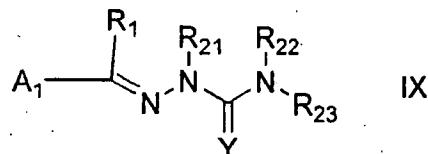
B₂ is an optionally substituted, saturated or partially unsaturated carbocycle or optionally substituted, saturated or partially unsaturated heterocycle.

- 14 -

Preferred B₁ and B₂ independently include cyclopentyl, cyclohexyl, cycloheptyl, tetrahydrofuryl, tetrahydropyranyl, pyrrolidinyl or piperidinyl.

Another preferred embodiment of the invention includes substituted semicarbazones and thiosemicarbazones represented by Formula IX:

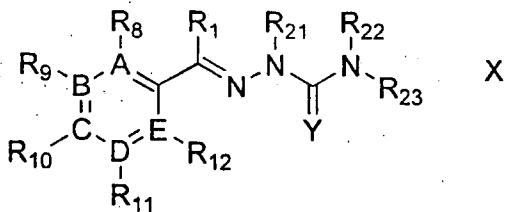
5



or a pharmaceutically acceptable salt or prodrug thereof, wherein

10 R₁, R₂₁-R₂₃, Y and A₁ are as defined previously with respect to Formula I. Novel compounds of Formula IX are those wherein a) one of R₂₁-R₂₃ is other than hydrogen; or b) A₁ is optionally substituted, saturated or partially unsaturated carbocycle or optionally substituted, saturated or partially unsaturated heterocycle; or c) when A₁ is phenyl, A₁ is substituted by more than two substituents which are other than hydrogen; or d) A₁ is a bicyclic 15 aryl.

Another preferred embodiment of the invention includes substituted semicarbazones and thiosemicarbazones represented by Formula X:



20

or a pharmaceutically acceptable salt or prodrug thereof, wherein

25 R₁, R₂₁-R₂₃, Y, A, B, C, D, E, and R₈-R₁₂ are as defined previously with respect to Formulae I and IV. Novel compounds of Formula X are those compounds wherein a) one of R₂₁-R₂₃ is other than hydrogen; or b) more than two of R₈-R₁₂ are other than hydrogen; or c) one of R₈ and R₉, or R₉ and R₁₀, or R₁₀ and R₁₁, or R₁₁ and R₁₂ are taken together with the carbon atoms to which they are attached to form a carbocycle or heterocycle. Examples of bridges formed by R₈ and R₉, or R₉ and R₁₀, or R₁₀ and R₁₁, or R₁₁ and R₁₂ taken together are —OCH₂O—, —OCF₂O—, —(CH₂)₃—, —(CH₂)₄—, —OCH₂CH₂O—, —CH₂N(R₇)CH₂—, —CH₂CH₂N(R₇)CH₂—,

- 15 -

—CH₂N(R₇)CH₂CH₂—, and —CH=CH—CH=CH—; where R₇ is hydrogen, alkyl or cycloalkyl.

Generally, preferred compounds of Formulae I-V and VII-X are those compounds where R₁ is hydrogen or alkyl, more preferably hydrogen, methyl or ethyl, and where R₂₁, R₂₂ and R₂₃ are independently hydrogen or C₁₋₄ alkyl.

Preferred values of X in Formulae I-V and VII-X are O and S. A preferred value of Y in Formulae I-V and VII-X is O.

Preferred values of R₃, R₄, R₅, R₆, and R₈-R₁₂, with respect to

Formulae II-V and VII-X include hydrogen, halo, C₁-C₆ haloalkyl, C₆-C₁₀ aryl, C₄-C₇ cycloalkyl, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₆-C₁₀ aryl(C₁-C₆)alkyl, C₆-C₁₀ aryl(C₂-C₆)alkenyl, C₆-C₁₀ aryl(C₂-C₆)alkynyl, C₁-C₆ hydroxyalkyl, nitro, amino, ureido, cyano, C₁-C₆ acylamido, hydroxy, thiol, C₁-C₆ acyloxy, azido, C₁-C₆ alkoxy, or carboxy. Alternatively, R₃ and R₄ or R₅ and R₆, or two adjacent R₈ through R₁₂ can form a bridge selected from the group consisting of —OCH₂O—, —(CH₂)₃—, —(CH₂)₄—, —OCH₂CH₂O—, —CH₂N(R₇)CH₂—, —CH₂CH₂N(R₇)CH₂—, —CH₂N(R₇)CH₂CH₂—, and —CH=CH—CH=CH—, where R₇ is hydrogen or C₁-C₆ alkyl. Most preferably, at least one, two or three of R₃, R₄, R₅, R₆ are hydrogen. Most preferably, at least one, two or three of R₈ through R₁₂ are hydrogen.

With respect to the novel methods of treatment of the present invention, an additional preferred subset of substituted semicarbazone compounds includes compounds of Formula I, wherein A₁ and A₂ are phenyl moieties, that are each independently substituted by one or two substituents independently selected from the group consisting of halogen, C₁₋₆ alkyl, C₃₋₈ cycloalkyl, cyano, C₁₋₆ alkoxy or C₆₋₁₀ aryloxy; R₁ is hydrogen, C₁₋₆ alkyl, C₃₋₈ cycloalkyl or C₆₋₁₀ aryl; Y is oxygen and X is oxygen or sulfur.

Useful compounds in this aspect of the present invention include:

4-phenoxybenzaldehyde semicarbazone;
4-(4-fluorophenoxy)benzaldehyde semicarbazone;
4-(4-chlorophenoxy)benzaldehyde semicarbazone;
4-(4-bromophenoxy)benzaldehyde semicarbazone;
4-(4-methoxyphenoxy)benzaldehyde semicarbazone;
4-(4-trifluoromethylphenoxy)benzaldehyde semicarbazone;
4-(4-methylphenoxy)benzaldehyde semicarbazone;
4-(3,4-difluorophenoxy)benzaldehyde semicarbazone;
4-(4-chloro-2-fluorophenoxy)benzaldehyde semicarbazone;

4-(4-nitrophenoxy)benzaldehyde semicarbazone;
4-(3-methylphenoxy)benzaldehyde semicarbazone;
4-(4-*t*-butylphenoxy)benzaldehyde semicarbazone;
4-(4-propylphenoxy)benzaldehyde semicarbazone;
5 4-(4-*s*-butylphenoxy)benzaldehyde semicarbazone;
4-(4-bromophenoxy)acetophenone semicarbazone;
4-(4-fluorophenoxy)acetophenone semicarbazone;
4-(4-chlorophenoxy)acetophenone semicarbazone;
4-(4-bromophenoxy)propiophenone semicarbazone;
10 4-(4-fluorophenoxy)propiophenone semicarbazone;
4-(4-chlorophenoxy)propiophenone semicarbazone;
4-phenylmercaptopbenzaldehyde semicarbazone;
4-(4-fluorophenylmercapto)benzaldehyde semicarbazone;
4-(4-chlorophenylmercapto)benzaldehyde semicarbazone;
15 4-cyclohexyloxybenzaldehyde semicarbazone;
4-cycloheptyloxybenzaldehyde semicarbazone;
4-(5-indanyloxy)benzaldehyde semicarbazone;
4-(6-quinolinylloxy)benzaldehyde semicarbazone;
4-(4-fluorophenoxy)-3-fluorobenzaldehyde semicarbazone;
20 4-(4-fluorophenoxy)cyclohexane-1-carboxaldehyde semicarbazone;
4-(tetrahydropyranlyloxy)benzaldehyde semicarbazone;
4-(1-methyl-4-piperidinoxy)benzaldehyde semicarbazone;
4-(4-fluorophenoxy)benzaldehyde 4'-methylsemicarbazone; and
4-(4-fluorophenoxy)benzaldehyde 2'-methylsemicarbazone.
25 Useful aryl groups are C₆₋₁₄ aryl, especially C₆₋₁₀ aryl. Typical C₆₋₁₄ aryl groups include phenyl, naphthyl, phenanthryl, anthracyl, indenyl, azulenyl, biphenyl, biphenylenyl and fluorenyl groups.
30 Useful cycloalkyl groups are C₃₋₈ cycloalkyl. Typical cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl and cycloheptyl.
Useful saturated or partially saturated carbocyclic groups are cycloalkyl groups as defined above, as well as cycloalkenyl groups, such as cyclopentenyl, cycloheptenyl and cyclooctenyl.
35 Useful halo or halogen groups include fluorine, chlorine, bromine and iodine.

Useful alkyl groups include straight-chained and branched C₁₋₁₀ alkyl groups, more preferably C₁₋₆ alkyl groups. Typical C₁₋₁₀ alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, *tert*-butyl, 3-pentyl, hexyl and octyl groups. Also contemplated is a trimethylene group substituted on two adjoining positions on the benzene ring of the compounds of the invention.

Useful alkenyl groups are C₂₋₆ alkenyl groups, preferably C₂₋₄ alkenyl. Typical C₂₋₄ alkenyl groups include ethenyl, propenyl, isopropenyl, butenyl, and *sec*-butenyl.

Useful alkynyl groups are C₂₋₆ alkynyl groups, preferably C₂₋₄ alkynyl. Typical C₂₋₄ alkynyl groups include ethynyl, propynyl, butynyl, and 2-butynyl groups.

Useful arylalkyl groups include any of the abovementioned C₁₋₁₀ alkyl groups substituted by any of the abovementioned C₆₋₁₄ aryl groups. Useful values include benzyl, phenethyl and naphthylmethyl.

Useful arylalkenyl groups include any of the abovementioned C₂₋₄ alkenyl groups substituted by any of the abovementioned C₆₋₁₄ aryl groups.

Useful arylalkynyl groups include any of the abovementioned C₂₋₄ alkynyl groups substituted by any of the abovementioned C₆₋₁₄ aryl groups. Useful values include phenylethynyl and phenylpropynyl.

Useful cycloalkylalkyl groups include any of the abovementioned C₁₋₁₀ alkyl groups substituted by any of the abovementioned cycloalkyl groups.

Useful haloalkyl groups include C₁₋₁₀ alkyl groups substituted by one or more fluorine, chlorine, bromine or iodine atoms, e.g. fluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, 1,1-difluoroethyl and trichloromethyl groups.

Useful hydroxyalkyl groups include C₁₋₁₀ alkyl groups substituted by hydroxy, e.g. hydroxymethyl, hydroxyethyl, hydroxypropyl and hydroxybutyl groups.

Useful alkoxy groups include oxygen substituted by one of the C₁₋₁₀ alkyl groups mentioned above.

Useful alkylthio groups include sulphur substituted by one of the C₁₋₁₀ alkyl groups mentioned above.

Useful acylamino groups are any C₁₋₆ acyl (alkanoyl) attached to an amino nitrogen, e.g. acetamido, propionamido, butanoylamido,

pentanoylamido, hexanoylamido as well as arylsubstituted C₂₋₆ substituted acyl groups.

Useful acyloxy groups are any C₁₋₆ acyl (alkanoyl) attached to an oxy (-O-) group, e.g. acetoxy, propionoyloxy, butanoyloxy, pentanoyloxy, hexanoyloxy and the like.

Useful saturated or partially saturated heterocyclic groups include tetrahydrofuranyl, pyranyl, piperidinyl, piperizinyl, pyrrolidinyl, imidazolidinyl, imidazolinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl, isochromanyl, chromanyl, pyrazolidinyl and pyrazolinyl groups.

Useful heterocycloalkyl groups include any of the abovementioned C₁₋₁₀ alkyl groups substituted by any of the abovementioned heterocyclic groups.

Useful heteroaryl groups include any one of the following: thienyl, benzo[b]thienyl, naphtho[2,3-b]thienyl, thianthrenyl, furyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxanthiinyl, 2H-pyrrolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, indolyl, indazolyl, purinyl, 4H-quinolizinyl, isoquinolyl, quinolyl, phthalzinyl, naphthyridinyl, quinozalinyl, cinnolinyl, pteridinyl, 5aH-carbazolyl, carbazolyl, (carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenazinyl, isothiazolyl, phenothiazinyl, isoxazolyl, furazanyl, phenoxazinyl, 1,4-dihydroquinoxaline-2,3-dione, 7-aminoisocoumarin, pyrido[1,2-a]pyrimidin-4-one, 1,2-benzoisoxazol-3-yl, 4-nitrobenzofurazan, benzimidazolyl, 2-oxindolyl and 2-oxobenzimidazolyl. Where the heteroaryl group contains a nitrogen atom in a ring, such nitrogen atom may be in the form of an N-oxide, e.g. a pyridyl N-oxide, pyrazinyl N-oxide, pyrimidinyl N-oxide and the like.

Useful heteroarylalkyl groups include any of the above-mentioned C₁₋₁₀ alkyl groups substituted by any of the above-mentioned heteroaryl groups.

Useful heteroarylalkenyl groups include any of the above-mentioned C₂₋₄ alkenyl groups substituted by any of the above-mentioned heteroaryl groups.

Useful heteroarylalkynyl groups include any of the above-mentioned C₂₋₄ alkynyl groups substituted by any of the above-mentioned heteroaryl groups.

Useful amino groups include $-\text{NH}_2$, $-\text{NHR}_{14}$, and $-\text{NR}_{14}\text{R}_{15}$, wherein R_{14} and R_{15} are C_{1-10} alkyl or cycloalkyl groups as defined above.

Useful aminocarbonyl groups are carbonyl groups substituted by $-\text{NH}_2$, $-\text{NHR}_{14}$, and $-\text{NR}_{14}\text{R}_{15}$, wherein R_{14} and R_{15} are C_{1-10} alkyl groups.

Optional substituents on any of the aryl, heterocyclic, heteroaryl, and cycloalkyl rings in Formulae I-V include any one of halo, haloalkyl, aryl, heterocycle, cycloalkyl, heteroaryl, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, cycloalkylalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxyalkyl, nitro, amino, ureido, cyano, acylamino, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, aminocarbonyl, and alkylthiol groups mentioned above. Preferred optional substituents include: halo, haloalkyl, hydroxyalkyl, aminoalkyl, nitro, alkyl, alkoxy and amino.

The term "lower" as employed herein refers to a group having up to 15 four carbon atoms. Saturated groups can have 1 to 4 carbon atoms. Unsaturated groups can have 2 to 4 carbon atoms.

Additional exemplary preferred compounds of Formula I include, without limitation:

- 20 4-(3,4-methylenedioxyphenoxy)benzaldehyde semicarbazone;
- 4-(2-pyridinoxy)benzaldehyde semicarbazone;
- 4-(3-pyridinoxy)benzaldehyde semicarbazone;
- 4-(4-pyridinoxy)benzaldehyde semicarbazone;
- 4-(4-chloro-2-pyridinoxy)benzaldehyde semicarbazone;
- 2-phenoxy pyridine-5-carboxaldehyde semicarbazone;
- 25 2-(4-chlorophenoxy)pyridine-5-carboxaldehyde semicarbazone;
- 2-(4-fluorophenoxy)pyridine-3-carboxaldehyde semicarbazone;
- 4-(2-pyrimidinoxy)benzaldehyde semicarbazone;
- 4-cyclohexyloxybenzaldehyde semicarbazone;
- 4-cycloheptyloxybenzaldehyde semicarbazone;
- 30 4-(5-indanyloxy)benzaldehyde semicarbazone;
- 4-(6-quinolinylloxy)benzaldehyde semicarbazone;
- 4-(4-fluorophenoxy)-3-fluorobenzaldehyde semicarbazone;
- 4-(4-fluorophenoxy)cyclohexane-1-carboxaldehyde semicarbazone;
- 4-(tetrahydropyranloxy)benzaldehyde semicarbazone;
- 35 4-(1-methyl-4-piperidinoxy)benzaldehyde semicarbazone;
- 4-(4-fluorophenoxy)benzaldehyde 4'-methylsemicarbazone;

4-(4-fluorophenoxy)benzaldehyde 2'-methylsemicarbazone; and compounds set forth in the Examples, but not listed here.

Certain of the compounds of Formula I may exist as E, Z-stereoisomers about the C=N double bond and the invention includes the mixture of isomers as well as the individual isomers that may be separated according to methods that are well known to those of ordinary skill in the art. Certain of the compounds of the present invention may exist as optical isomers and the invention includes both the racemic mixtures of such optical isomers as well as the individual enantiomers that may be separated according to methods that are well known to those of ordinary skill in the art.

Examples of pharmaceutically acceptable addition salts include inorganic and organic acid addition salts such as hydrochloride, hydrobromide, phosphate, sulphate, citrate, lactate, tartrate, maleate, fumarate, mandelate, acetic acid, dichloroacetic acid and oxalate.

Examples of prodrugs include esters or amides of Formula I with R₃-R₆ as hydroxyalkyl or aminoalkyl, and these may be prepared by reacting such compounds with anhydrides such as succinic anhydride.

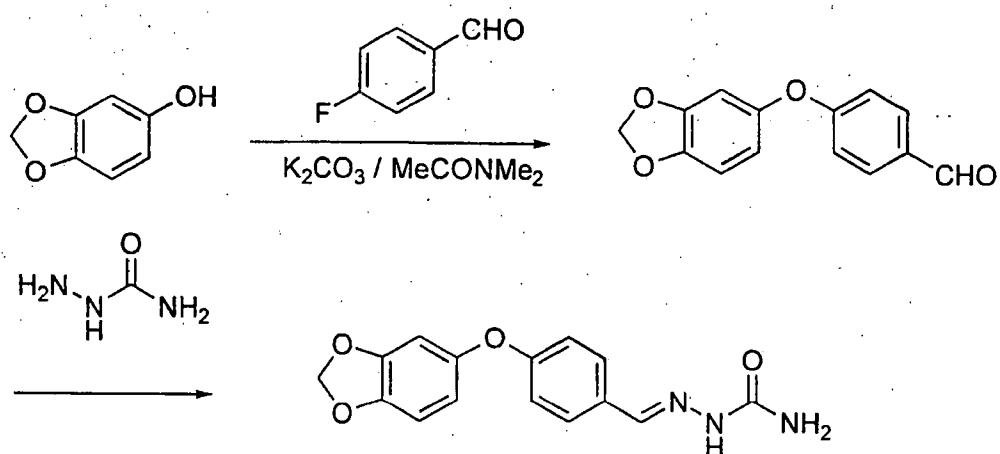
The invention is also directed to a method for treating disorders responsive to the blockade of sodium channels in animals suffering thereof. Particular preferred embodiments of the substituted semicarbazones for use in method of this invention are represented by previously defined Formula I.

The compounds of this invention may be prepared using methods known to those skilled in the art, or by the novel methods of this invention. The methods described in PCT published application WO96/40628, can be employed to synthesize compounds within the scope of the invention.

Compounds with Formulae I-III can be prepared as illustrated by exemplary reactions in Scheme 1.

- 21 -

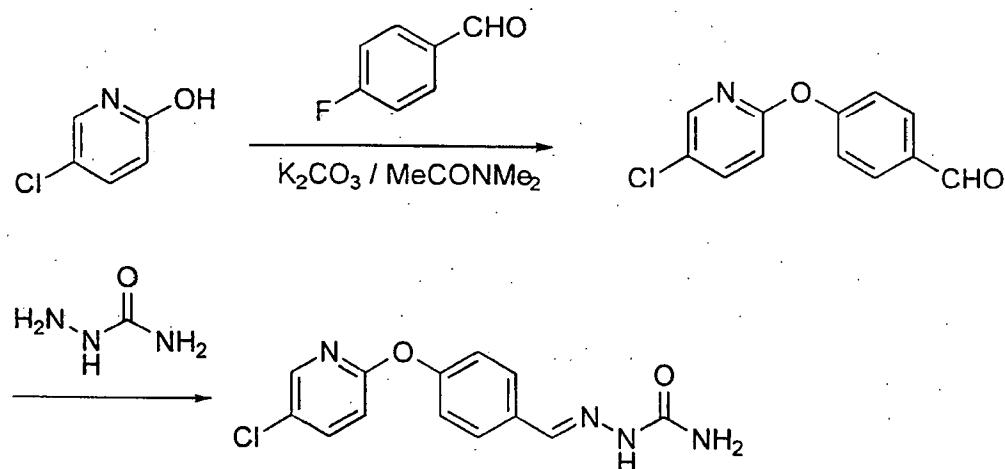
Scheme 1



Compounds with Formulae I-II and IV can be prepared as illustrated by exemplary reactions in Scheme 2.

5

Scheme 2

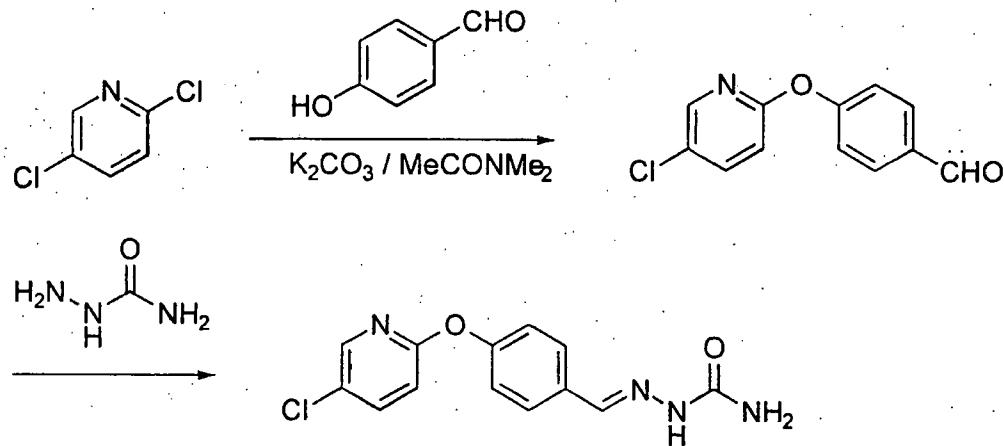


Alternatively, compounds with Formulae I-II and IV can be prepared as illustrated by exemplary reactions in Scheme 3.

10

- 22 -

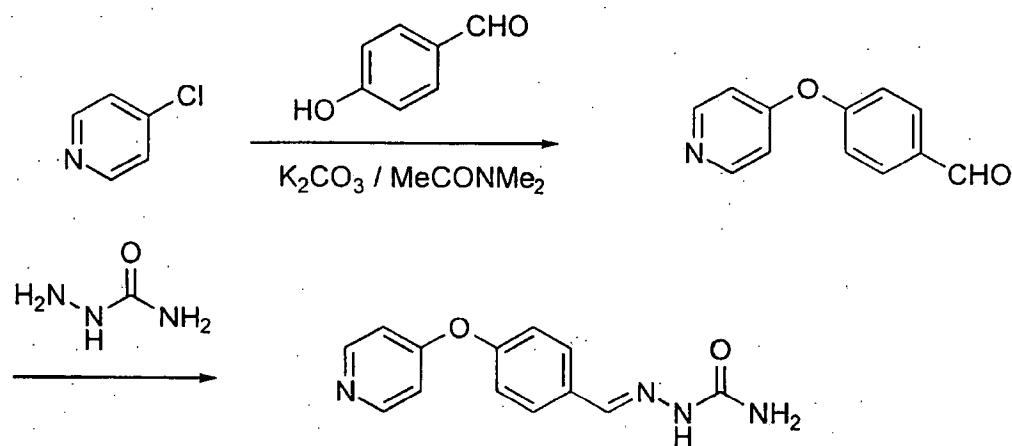
Scheme 3



Compounds with Formulae I-II and IV also can be prepared as illustrated by exemplary reactions in Schemes 4 and 5.

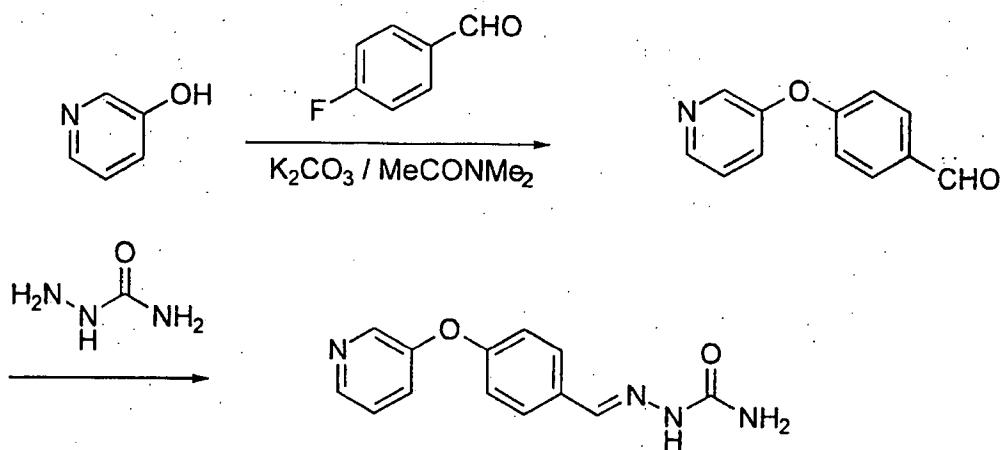
5

Scheme 4



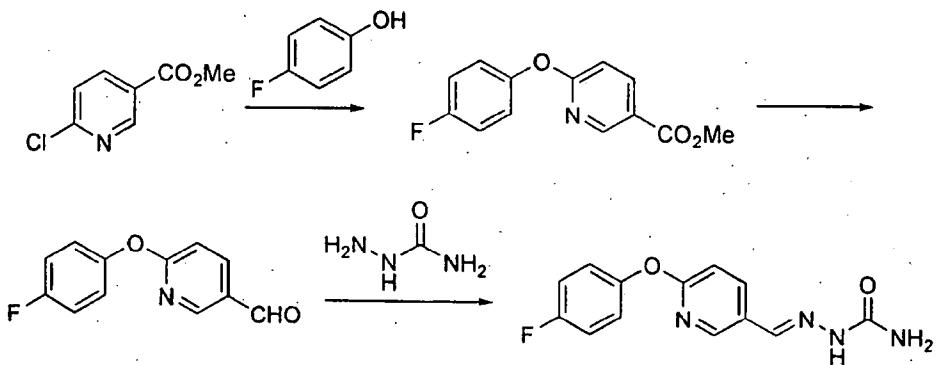
- 23 -

Scheme 5



5 Compounds with Formulae I, III and V can be prepared as illustrated by exemplary reactions in Scheme 6.

Scheme 6

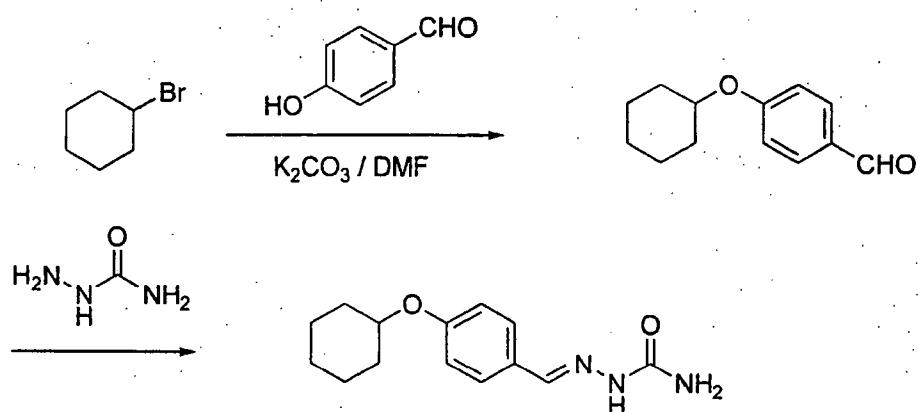


10 Compounds within the scope of Formula VI can be prepared according to the methods described in PCT International Published Application WO94/06758.

Compounds with Formula VIII can be prepared as illustrated by exemplary reactions in Scheme 7.

- 24 -

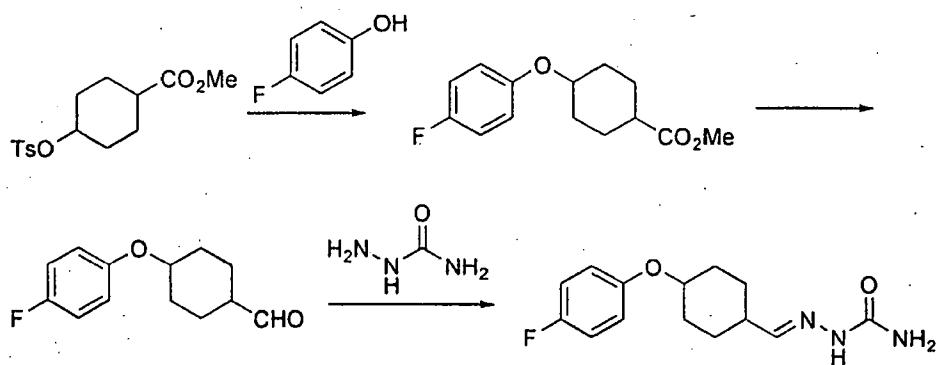
Scheme 7



5

Compounds with Formula IX can be prepared as illustrated by exemplary reactions in Scheme 8.

Scheme 8



10

The compounds of the present invention were assessed by electrophysiological assays in dissociated hippocampal neurons for sodium channel blocker activity. These compounds also could be assayed for binding to the neuronal voltage-dependent sodium channel using rat forebrain membranes and [3H]BTX-B.

15

Sodium channels are large transmembrane proteins that are expressed in various tissues. They are voltage sensitive channels and are responsible for the rapid increase of Na^+ permeability in response to depolarization associated

with the action potential in many excitable cells including muscle, nerve and cardiac cells.

One aspect of the present invention is the discovery of the mechanism of action of the compounds herein described as specific Na^+ channel blockers. 5 In one aspect of the present invention it has been discovered that compounds disclosed in International published applications WO 94/06758 and WO 96/40628 are specific Na^+ channel blockers. Based upon the discovery of this mechanism, these compounds, as well as novel compounds described herein, are contemplated to be useful in treating or preventing neuronal loss due to 10 focal or global ischemia, and in treating or preventing neurodegenerative disorders including ALS, anxiety, and epilepsy. They are also useful in treating or preventing otoneurotoxicity including acute and progressive hearing loss and tinnitus. They are also expected to be effective in treating, preventing or ameliorating neuropathic pain, surgical pain and chronic pain. 15 The compounds are also expected to be useful as antiarrhythmics, anesthetics and antimanic depressants.

The present invention is directed to compounds of Formulae I and VI that are blockers of voltage-sensitive sodium channels. According to the 20 present invention, those compounds having preferred sodium channel blocking properties exhibit an IC_{50} of about 100 μM or less in the electrophysiological assay described herein. Preferably, the compounds of the present invention exhibit an IC_{50} of 10 μM or less. Most preferably, the compounds of the 25 present invention exhibit an IC_{50} of about 1.0 μM or less. Substituted semicarbazones disclosed in WO 94/06758 and WO 96/40628, as well as novel compounds of the present invention, may be tested for their Na^+ channel blocking activity by the following electrophysiological and binding assays.

Electrophysiological Assay:

30 ***Cell preparation:*** Acute cultures of rat hippocampal neurons were prepared daily using a modification of procedures described previously (Kuo and Bean, *Mol. Pharm.* 46:716-725 (1994)). Briefly, hippocampi were isolated from 3-11 day old rat pup brains (Sprague-Dawley; Charles River) and were sectioned, by hand, into 0.5 - 1 mm thick transverse slices 35 (Whittemore and Koerner, *Eur. J. Pharm.* 192:435-438 (1991)). Slices were incubated for at least 30 min at room temperature (20 - 24 °C) in an

oxygenated medium (124 mM NaCl, 3.3 mM KCl, 2.4 mM MgSO₄, 2.5 mM CaCl₂, 1.2 mM KH₂PO₄, 26 mM NaHCO₃, pH = 7.4) continuously bubbled with 5% CO₂ / 95 % O₂. Prior to recording, 4-5 slices were transferred to an oxygenated dissociation medium (82 mM NaSO₄, 30 mM K₂SO₄, 3 mM MgCl₂, 2 mM HEPES, 26 mM NaHCO₃, 0.001% phenol red, pH = 7.4) containing 3 mg / mL protease XXIII (Sigma, St. Louis, MO) and incubated for 10 - 15 min at 37°C, while continuously bubbling with 5 % CO₂ / 95 % O₂. Enzymatic digestion was terminated by transferring the slices to dissociation medium without bicarbonate, supplemented with 1 mg / mL bovine serum albumin and 1 mg / mL trypsin inhibitor (Sigma, St. Louis, MO). Slices were then transferred to a 35 mm culture dish containing dissociation medium without bicarbonate, and triturized with a fire-polished glass Pasteur pipette to release single cells. Cells were allowed to settle in this dish for ~30 minutes and were then used for making electrical recordings.

Patch-clamp recordings of voltage-sensitive Na⁺ currents: Whole-cell voltage-clamp recordings were made using conventional patch-clamp technique (Hamill *et al.*, *Pfluegers Arch.* 391:85-100 (1981)) with an Axopatch 200A amplifier (Axon Instruments, Foster City, CA). Recordings were made within 2-3 hours after neuron dissociation. The recording chamber was continuously superfused with Tyrode's solution (156 mM NaCl, 3.5 mM KCl, 2 mM CaCl₂, 5 mM NaHCO₃, 10 mM HEPES, 10 mM glucose, pH 7.4) at a speed of about 1 ml/min. Thin-walled pipettes were pulled from 100- μ l Clay Adams Accu-Fill 90 Micropet disposable pipettes (Becton, Dickenson and Company, Parsipanny, NJ), fire-polished and sylgarded (Dow-Corning, Midland, MI). The pipette resistances ranged from 1 to 3 M Ω when the pipettes were filled with internal solution containing (in mM): 130 CsF, 20 NaCl, 1 CaCl₂, 2 MgCl₂, 10 EGTA, 10 HEPES, pH adjusted to 7.4 with CsOH. Drugs and intervening wash-outs were applied through a linear array of flow pipes (Drummond Microcaps, 2- μ l, 64-mm length). Compounds are dissolved in dimethylsulfoxide (DMSO) to make a 10 mM stock solution, which was subsequently diluted into Tyrode's solution to give final concentrations of 0.1-20 μ M. At the highest (1%) concentration, DMSO inhibited the size of Na⁺ current only slightly. Currents were recorded at room temperature (22-25°C), filtered at 5 kHz with 4-pole Bessel filter, digitized at 20-50- μ s intervals, and stored using Digidata 1200 analog/digital interface with Pclamp6/Clampex software (Axon Instruments). Residual series

resistance ranged from 0.4 to 0.8 M Ω after partial compensation (typically ~90%). The inhibitory potency of drugs was assessed by measuring reductions in the peak amplitude of Na⁺ currents induced by increasing concentrations of compounds tested. Na⁺ currents were elicited by stepping membrane voltage from holding potentials over the range -100 mV to -50 mV, to a pulse potential of -10 mV. The test pulse duration was 5-10 msec, repeated at a frequency \leq 1 Hz. Concentration-inhibition curves were fitted with equation 1:

10 $I/I_{control} = 1/(1 + ([compound]/IC_{50}))$

Eq. 1

where $I_{control}$ is the maximal Na⁺ current in the absence of antagonist, [compound] is the drug concentration, and IC₅₀ is the concentration of compound that produces half maximal inhibition.

15

Binding Assay:

20
25

The ability of compounds of the present invention to modulate either site 1 or site 2 of the Na⁺ channel was determined following the procedures fully described in Yasushi, *J. Biol. Chem.* 261:6149-6152 (1986) and Creveling, *Mol. Pharmacol.* 23:350-358 (1983), respectively. Rat forebrain membranes were used as sources of Na⁺ channel proteins. The binding assays were conducted in 130 (M choline chloride at 37°C for 60-minute incubation with [³H] saxitoxin and [³H] batrachotoxin as radioligands for site 1 and site 2, respectively.

30 The compounds of the present invention may be tested for *in vivo* anticonvulsant activity after iv or ip injection using a number of anticonvulsant tests in mice (audiogenic seizure model in DBA-2 mice, pentylenetetrazol-induced seizures in mice, maximum electroshock seizure test (MES)).

35 The compounds may be tested for their neuroprotective activity after focal and global ischemia produced in rats or gerbils according to the procedures described in Buchan *et al.* (*Stroke, Suppl.* 148-152 (1993)) and Sheardown *et al.* (*Eur. J. Pharmacol.* 236:347-353 (1993)) and Graham *et al.* (*J. Pharmacol. Exp. Therap.* 276:1-4 (1996)).

35 The compounds may be tested for their neuroprotective activity after traumatic spinal cord injury according to the procedures described in Wrathall

et. al. (Exp. Neurology 137:119-126 (1996)) and Iwasaki et. al. (J. Neuro Sci. 134:21-25 (1995)).

5 Compositions within the scope of this invention include all compositions wherein the compounds of the present invention are contained in an amount which is effective to achieve its intended purpose. While individual needs vary, determination of optimal ranges of effective amounts of each component is within the skill of the art. Typically, the compounds may be administered to mammals, e.g. humans, orally at a dose of 0.0025 to 50 mg/kg, or an equivalent amount of the pharmaceutically acceptable salt thereof, per day of the body weight of the mammal being treated for epilepsy, 10 neurodegenerative diseases, anesthetic, arrhythmia, manic depression, and pain. For intramuscular injection, the dose is generally about one-half of the oral dose.

15 In the method of treatment or prevention of neuronal loss in global and focal ischemia, brain and spinal cord trauma, hypoxia, hypoglycemia, status epilepsy and surgery, the compound can be administrated by intravenous injection at a dose of about 0.025 to about 10 mg/kg.

20 The unit oral dose may comprise from about 0.01 to about 50 mg, preferably about 0.1 to about 10 mg of the compound. The unit dose may be administered one or more times daily as one or more tablets each containing from about 0.1 to about 10, conveniently about 0.25 to 50 mg of the compound or its solvates.

25 In addition to administering the compound as a raw chemical, the compounds of the invention may be administered as part of a pharmaceutical preparation containing suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the compounds into preparations which can be used pharmaceutically. Preferably, the preparations, particularly those preparations which can be administered orally and which can be used for the preferred type of administration, such as 30 tablets, dragees, and capsules, and also preparations which can be administered rectally, such as suppositories, as well as suitable solutions for administration by injection or orally, contain from about 0.01 to 99 percent, preferably from about 0.25 to 75 percent of active compound(s), together with the excipient.

35 Also included within the scope of the present invention are the non-toxic pharmaceutically acceptable salts of the compounds of the present invention. Acid addition salts are formed by mixing a solution of the

particular semicarbazones of the present invention with a solution of a pharmaceutically acceptable non-toxic acid such as hydrochloric acid, fumaric acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid, phosphoric acid, oxalic acid, dichloroacetic acid, and the like. Basic salts 5 are formed by mixing a solution of the particular semicarbazones of the present invention with a solution of a pharmaceutically acceptable non-toxic base such as sodium hydroxide, potassium hydroxide, choline hydroxide, sodium carbonate and the like.

10 The pharmaceutical compositions of the invention may be administered to any animal which may experience the beneficial effects of the compounds of the invention. Foremost among such animals are mammals, e.g., humans, although the invention is not intended to be so limited.

15 The pharmaceutical compositions of the present invention may be administered by any means that achieve their intended purpose. For example, administration may be by parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, or buccal routes. Alternatively, or concurrently, administration may be by the oral route. The dosage administered will be dependent upon the age, health, and weight of the 20 recipient, kind of concurrent treatment, if any, frequency of treatment, and the nature of the effect desired.

25 The pharmaceutical preparations of the present invention are manufactured in a manner which is itself known, for example, by means of conventional mixing, granulating, dragee-making, dissolving, or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipients, optionally grinding the resulting mixture and processing the mixture of granules, after adding suitable auxiliaries, if desired or necessary, to obtain tablets or dragee cores.

30 Suitable excipients are, in particular, fillers such as saccharides, for example lactose or sucrose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, as well as binders such as starch paste, using, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinyl pyrrolidone. If desired, disintegrating agents may be added 35 such as the above-mentioned starches and also carboxymethyl-starch, cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof, such as

5 sodium alginate. Auxiliaries are, above all, flow-regulating agents and lubricants, for example, silica, talc, stearic acid or salts thereof, such as magnesium stearate or calcium stearate, and/or polyethylene glycol. Dragee cores are provided with suitable coatings which, if desired, are resistant to gastric juices. For this purpose, concentrated saccharide solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures. In order to produce coatings resistant to 10 gastric juices, solutions of suitable cellulose preparations such as acetylcellulose phthalate or hydroxypropymethyl-cellulose phthalate, are used. Dye stuffs or pigments may be added to the tablets or dragee coatings, for example, for identification or in order to characterize combinations of active 15 compound doses.

15 Other pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer such as glycerol or sorbitol. The push-fit capsules can contain the active compounds in the form of granules which may be mixed with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds are preferably dissolved or suspended in suitable liquids, such as fatty oils, or liquid paraffin. In addition, stabilizers may be added.
20

Possible pharmaceutical preparations which can be used rectally include, for example, suppositories, which consist of a combination of one or more of the active compounds with a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, or paraffin hydrocarbons. In addition, it is also possible to use gelatin rectal capsules which consist of a combination of the active compounds with a base. Possible base materials include, for example, liquid triglycerides, polyethylene glycols, or paraffin hydrocarbons.

30 Suitable formulations for parenteral administration include aqueous
solutions of the active compounds in water-soluble form, for example, water-
soluble salts and alkaline solutions. In addition, suspensions of the active
compounds as appropriate oily injection suspensions may be administered.
35 Suitable lipophilic solvents or vehicles include fatty oils, for example, sesame
oil, or synthetic fatty acid esters; for example, ethyl oleate or triglycerides or
polyethylene glycol-400 (the compounds are soluble in PEG-400). Aqueous

injection suspensions may contain substances which increase the viscosity of the suspension include, for example, sodium carboxymethyl cellulose, sorbitol, and/or dextran. Optionally, the suspension may also contain stabilizers.

5 The following examples are illustrative, but not limiting, of the method and compositions of the present invention. Other suitable modifications and adaptations of the variety of conditions and parameters normally encountered in clinical therapy and which are obvious to those skilled in the art are within the spirit and scope of the invention.

10

Example 1

4-(4-Chloro-2-pyridinoxy)benzaldehyde semicarbazone

a) **4-(4-Chloro-2-pyridinoxy)benzaldehyde:** To a solution of 4-fluorobenzaldehyde (3.6 g, 29 mmol) in N,N-dimethylacetamide (25 mL) was added 5-chloro-2-pyridinol (4.1 g, 32 mmol) and K₂CO₃ (4.1 g, 30 mmol) at room temperature under argon. The mixture was heated to reflux for 4 h, cooled to room temperature, diluted with ethyl acetate (150 mL), washed with water and brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by chromatography to yield the title compound as a white solid (0.59 g, 2.5 mmol, 8%). ¹H NMR (CDCl₃): δ 9.99 (s, 1H), 8.16 (s, 1H), 7.94 (d, J = 7.7, 2H), 7.27 (d, J = 7.7, 2H), 7.71 (d, J = 8.6, 1H), 6.99 (d, J = 8.6, 1H).

b) **4-(4-Chloro-2-pyridinoxy)benzaldehyde semicarbazone:** To a solution of 4-(4-chloro-2-pyridinoxy)benzaldehyde (330 mg, 1.41 mmol) in ethanol (10 mL) was added a solution of semicarbazide hydrochloride (213 mg, 1.84 mmol) and sodium acetate trihydrate (224 mg, 1.65 mmol) in water (5 mL). The mixture was stirred at room temperature for 30 min., and the resulting solid was collected by filtration, washed with water and dried in vacuo to yield the title compound as a white solid (400 mg, 1.36 mmol, 96%), mp: 231-233°C. ¹H NMR (DMSO-*d*₆): δ 10.22 (s, 1H), 8.22 (d, J = 2.5, 1H), 7.97 (dd, J = 2.5, 8.7, 1H), 7.85 (s, 1H), 7.77 (d, J = 8.7, 2H), 7.15 (d, J = 8.7, 2H), 7.12 (d, J = 8.7, 1H), 6.47 (s, 2H).

- 32 -

Example 2

4-(4-Pyridinoxy)benzaldehyde semicarbazone

a) **4-(4-Pyridinoxy)benzaldehyde:** To a solution of 4-hydroxybenzaldehyde (2.8 g, 23 mmol) in N,N-dimethylacetamide (30 mL) was added 4-chloropyridine hydrochloride (3.4 g, 23 mmol) and K₂CO₃ (5.0 g, 36 mmol) at room temperature under argon. The mixture was heated to reflux for 6 h, cooled to room temperature, diluted with ethyl acetate (75 mL), washed with water, 2N NaOH and brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by chromatography to yield the title compound as a colorless liquid (0.57 g, 2.9 mmol, 13%). ¹H NMR (CDCl₃): δ 10.00 (s, 1H), 8.56 (d, J = 6.0, 2H), 7.96 (d, J = 8.5, 2H), 7.23 (d, J = 8.5, 2H), 6.93 (d, J = 6.0, 2H).

b) **4-(4-Pyridinoxy)benzaldehyde semicarbazone:** To a solution of 4-(4-pyridinoxy)benzaldehyde (570 mg, 2.86 mmol) in ethanol (10 mL) was added a solution of semicarbazide hydrochloride (350 mg, 3.03 mmol) and sodium acetate (235 mg, 2.86 mmol) in water (5 mL). The mixture was stirred at room temperature for 30 min., diluted with ethyl acetate (75 mL), washed with 2N NaOH, water and brine, dried over Na₂SO₄, concentrated in vacuo to yield the title compound as a white solid (720 mg, 2.77 mmol, 97%), mp: 212-213°C. ¹H NMR (DMSO-d₆): δ 10.29 (s, 1H), 8.49 (d, J = 4.9, 2H), 7.87 (s, 1H), 7.84 (d, J = 8.5, 2H), 7.19 (d, J = 8.5, 2H), 6.96 (d, J = 4.9, 2H), 6.53 (s, 2H).

25 **4-(2-Pyridinoxy)benzaldehyde semicarbazone** is prepared as described for 4-(4-pyridinoxy)benzaldehyde semicarbazone.

2-Phenoxy-5-carboxaldehyde semicarbazone, 2-(4-chlorophenoxy)pyridine-5-carboxaldehyde semicarbazone and 2-(4-fluorophenoxy)pyridine-3-carboxaldehyde semicarbazone are prepared from the corresponding aldehydes as described for 4-(5-indanoxy)benzaldehyde semicarbazone.

- 33 -

Example 3

4-(3-Pyridinoxy)benzaldehyde semicarbazone

a) **4-(3-pyridinoxy)benzaldehyde:** A mixture of 4.02 g (42.3 mmol) of 3-hydroxypyridine, 5.40 g (43.5 mmol) of 4-fluorobenzaldehyde and 5.92 g (42.8 mmol) of anhydrous potassium carbonate in dimethylacetamide (40 mL) was refluxed (~ 180°C) overnight. It was cooled to room temperature, and poured into water (50 mL). The mixture was extracted with 1:1 hexane/ethyl acetate (2 x 50 mL). The combined extract was washed with water (50 mL), 0.4 N NaOH (50 mL) and water (50 mL), dried (NaSO₄) and evaporated to leave 7.62 g of oil, which was used for the next reaction.

b) **4-(3-Pyridinoxy)benzaldehyde semicarbazone:** To a solution of 659 mg (3.31 mmol) of the oil in absolute ethanol (10 mL) was added dropwise a solution of 369 mg (3.31 mmol) of semicarbazide hydrochloride and 274 mg (3.31 mmol) of sodium acetate in water (3 mL). The solution was stirred at room temperature for 2 h to give white precipitates. The mixture was filtered and the solid was washed with methanol (1 mL), dried to leave 320 mg (37%) of the title compound as white solid. More solid was observed in the filtrate. It was filtered and washed by water (2 mL), dried to leave 302 mg (35%) of the title compound as white solid, mp 160-162°C. ¹H NMR (DMSO-d₆): δ 10.23 (s, 1H), 8.39 (m, 2H), 7.82 (s, 1H), 7.76 (d, J = 8.4, 2H), 7.47 (m, 2H), 7.05 (d, J = 8.4, 2H), 6.48 (s, 2H).

Example 4

4-(3,4-methylenedioxypheoxy)benzaldehyde semicarbazone

a) **4-(3,4-methylenedioxypheoxy)benzaldehyde:** To a solution of 4-fluorobenzaldehyde (1.9 g, 15 mmol) in N,N-dimethylacetamide (25 mL) was added sesamol (2.1 g, 15 mmol) and K₂CO₃ (2.2 g, 16 mmol) at room temperature under argon. The mixture was heated to reflux for 5 h, cooled to room temperature, diluted with ethyl acetate (100 mL), washed with water and brine, dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by chromatography to yield the title compound as a white solid (1.7 g, 7.0 mmol, 46%). ¹H NMR (CDCl₃): δ 9.91 (s, 1H), 7.84 (d, J = 8.8, 2H), 7.03 (d, J = 8.8, 2H), 6.82 (d, J = 8.3, 1H), 6.62 (d, J = 2.3, 1H), 6.56 (dd, J = 2.3, 8.3, 1H), 6.02 (s, 2H).

b) **4-(3,4-methylenedioxyphenoxy)benzaldehyde semicarbazone:** To a solution of 4-(3,4-methylenedioxyphenoxy)benzaldehyde (1.7 g, 7.0 mmol) in ethanol (40 mL) was added a solution of semicarbazide hydrochloride (0.82 g, 7.1 mmol) and sodium acetate (0.55 g, 6.7 mmol) in water (10 mL). The mixture was stirred at room temperature for 30 min. The resulting white solid was collected by filtration, washed with water and dried in vacuo to yield the title compound (1.2 g, 4.0 mmol, 57%), mp: 225-226°C. ¹H NMR (DMSO-*d*₆): δ 10.17 (s, 1H), 7.80 (s, 1H), 7.70 (d, *J* = 8.7, 2H), 6.93 (d, *J* = 8.3, 1H), 6.92 (d, *J* = 8.7, 2H), 6.77 (d, *J* = 2.4, 1H), 6.53 (dd, *J* = 2.4, 8.3, 1H), 6.44 (s, 2H), 6.06 (s, 2H).

Example 5

4-Cyclohexyloxybenzaldehyde semicarbazone

15 **a) 4-Cyclohexyloxybenzaldehyde:** A mixture of 4-hydroxybenzaldehyde (5.2 g), cyclohexyl bromide (25 mL), and potassium carbonate (10 g) in DMF (25 mL) was heated under nitrogen at 90 °C for two days. After cooling, the mixture was diluted with 1:1 hexane/EtOAc (100 mL), washed with water (2 x 50 mL), 2N NaOH (3 x 15 mL), water (20 mL) and brine (20 mL), dried over Na₂SO₄, and concentrated *in vacuo* to yield the title compound as an oil (2.1 g, 24%). ¹H NMR (CDCl₃): δ 9.86 (s, 1H), 7.82 (d, J = 8.5, 2H), 6.98 (d, J = 8.5, 2H), 4.38 (m, 1H), 2.01-1.38 (m, 10H).

25 **b) 4-Cyclohexyloxybenzaldehyde semicarbazone:** To a solution of 4-cyclohexyloxybenzaldehyde (2.1 g) in ethanol (50 mL) was added a solution of semicarbazide hydrochloride (1.24 g) and sodium acetate (0.87 g) in water (20 mL) at room temperature. The mixture was stirred for 30 min, and the resulting solid was collected by filtration, washed with water (3 x 50 mL) and dried *in vacuo* to yield the title compound as a white solid (2.2 g, 72%), mp: 215 -217°C. ^1H NMR (DMSO- d_6): δ 10.08 (s, 1H), 7.61 (d, J = 8.5, 2H), 6.92 (d, J = 8.5, 2H), 6.41 (s, 2H), 4.38 (m, 1H), 1.91-1.24 (m, 10H).

Example 6

4-Cycloheptyloxybenzaldehyde semicarbazone

35 a) **4-Cycloheptyloxybenzaldehyde:** A mixture of 4-hydroxybenzaldehyde (1.5 g), cycloheptyl bromide (3.5 mL), and potassium carbonate (2.4 g) in *N,N*-dimethyl acetamide (40 mL) was refluxed under nitrogen for 17 h. After

- 35 -

cooling, the mixture was diluted with 1:1 hexane/EtOAc (80 mL), washed with water (2 x 30 mL), 2N NaOH (2 x 20 mL), water (30 mL) and brine (20 mL), dried over Na_2SO_4 , and concentrated *in vacuo* to yield the title compound as an oil (1.7 g, 63%). ^1H NMR (CDCl_3): δ 9.86 (s, 1H), 7.80 (m, 2H), 6.91 (m, 2H), 4.38 (m, 1H), 2.04-1.52 (m, 12H).

5 b) **4-Cycloheptyloxybenzaldehyde semicarbazone:** To a solution of 4-cycloheptyloxybenzaldehyde (1.7 g) in ethanol (20 mL) was added a solution of semicarbazide hydrochloride (0.96 g) and sodium acetate (0.69 g) in water (10 mL) at room temperature. The mixture was stirred for 30 min, and the resulting solid was collected by filtration, washed with water (3 x 30 mL) and dried *in vacuo* to yield the title compound as a white solid (1.7 g, 79%), mp: 10 215-216°C. ^1H NMR ($\text{DMSO-}d_6$): δ 10.07 (s, 1H), 7.76 (s, 1H), 7.61 (d, J = 8.4, 2H), 6.89 (d, J = 8.4, 2H), 6.40 (s, 2H), 4.54 (m, 1H), 1.98-1.47 (m, 12H).

15

Example 7

4-(5-Indanoxy)benzaldehyde semicarbazone

a) **4-(5-indanoxy)benzaldehyde:** A mixture of 4-fluorobenzaldehyde (4.1 mL), 5-indanol (5.2 g), and potassium carbonate (5.5 g) in *N,N*-dimethylacetamide (30 mL) was refluxed under nitrogen for 17 h. After cooling, the mixture was diluted with 1:1 hexane/EtOAc (100 mL), washed with water (2 x 30 mL), 2N NaOH (20 mL), water (30 mL) and brine (20 mL), dried over Na_2SO_4 , and concentrated *in vacuo* to yield the title compound as an oil (6.2 g, 68%). ^1H NMR (CDCl_3): δ 9.91 (s, 1H), 7.83 (d, J = 8.8, 2H), 7.23 (d, J = 7.8, 1H), 7.04 (d, J = 8.8, 2H), 6.94 (s, 1H), 6.85 (d, J = 7.8, 1H), 2.92 (t, J = 7.2, 4H), 2.13 (m, 2H).

20

25

30

35

b) **4-(5-indanoxy)benzaldehyde semicarbazone:** To a solution of 4-(5-indanoxy)benzaldehyde (6.2 g) in ethanol (100 mL) was added a solution of semicarbazide hydrochloride (3.2 g) and sodium acetate (2.3 g) in water (50 mL) at room temperature. The mixture was stirred for 1 h, and the resulting solid was collected by filtration, washed with water (3 x 100 mL) and dried *in vacuo* to yield the title compound as a pale yellow solid (7.5 g, 97%), mp: 218-220°C. ^1H NMR ($\text{DMSO-}d_6$): δ 10.19 (s, 1H), 7.80 (s, 1H), 7.70 (d, J = 8.7, 2H), 7.24 (d, J = 8.1, 1H), 6.94 (d, J = 8.7, 2H), 6.92 (s, 1H), 6.82 (d, J = 8.1, 1H), 6.45 (s, 2H), 2.84 (t, J = 7.5, 4H), 2.05 (m, 2H).

Example 8

4-(4-Fluorophenoxy)benzaldehyde 4'-Methylsemicarbazone

a) **4-Methyl Semicarbazide:** A solution of methyl isocyanate (5.74 mmol, 0.34 mL) in benzene (5 mL) was added dropwise over 10 min to a stirred solution of hydrazine hydrate (0.18 mL, 5.74 mmol) in EtOH (10 mL). Additional benzene (5 mL) was added, and the resulting solution was stirred at rt for 1 h. The precipitate was removed by vacuum filtration and the filtrate was concentrated to give 289 mg (57%) of the title compound as a white solid:
10 ^1H NMR (DMSO- d_6) δ 2.55 (d, 3H), 4.01 (s, 2H), 6.22 (bs, 1H), 6.86 (s, 1H).

b) **4-(4-Fluorophenoxy)benzaldehyde 4'-Methylsemicarbazone:** A solution of 4-methyl semicarbazide (289 mg, 3.28 mmol) and the 4-(4-fluorophenoxy)benzaldehyde (355 mg, 1.64 mmol) in EtOH (20 mL) was stirred at rt overnight. To the solution was added H_2O (100 mL), and the mixture was allowed to sit in an ice-bath for 30 min. The precipitate was collected by vacuum filtration to afford 462 mg (98%) of the title compound as a white powder: mp 168-169°C; ^1H NMR (DMSO- d_6) δ 2.67 (d, 3H), 6.91-6.97 (m, 3H), 7.07-7.11 (m, 2H), 7.21-7.26 (m, 2H), 7.15 (d, 2H), 7.78 (s, 1H), 10.26 (s, 1H).

Example 9

4-(4-Fluorophenoxy)benzaldehyde 2'-Methylsemicarbazone

To a solution of sodium cyanate (1.43 g) in water (15 mL) was added 25 methylhydrazine (1.0 mL). The mixture was stirred at room temperature for 17 h and then acetic acid (2 mL) was added. The mixture was further stirred at room temperature for 3 h and then was added to a solution of 4-(4-fluorophenoxy)benzaldehyde (1.1 g) in ethanol (30 mL) at rt. After 2 h stirring, the resulting solid was collected by filtration, washed with water (3 x 30 20 mL) and dried *in vacuo* to yield the title compound as a white solid (1.4 g, 96%), mp: 153-154°C. ^1H NMR (DMSO- d_6): δ 7.86 (d, J = 8.4, 2H), 7.67 (s, 1H), 7.29-7.09 (m, 4H), 6.99 (d, J = 8.4, 2H), 6.65 (br s, 2H), 3.22 (s, 3H).

Example 10**4-(Cyclohexylmethoxy)benzaldehyde semicarbazone**

a) **4-(Cyclohexylmethoxy)benzaldehyde.** A mixture of 4-hydroxybenzaldehyde (1.41 g, 11.5 mmol), (bromomethyl)cyclohexane (1.0 mL, 11.5 mmol), and potassium carbonate (3.2 g) in *N,N*-dimethylacetamide (25 mL) was refluxed for 17 h under nitrogen. After cooling, the mixture was diluted with 1:1 hexane/EtOAc (75 mL), washed with water (2 x 30 mL), 2N NaOH (20 mL), water (30 mL) and brine (20 mL), dried over Na₂SO₄, concentrated *in vacuo* to yield the title compound as a brown oil (1.6 g, 7.3 mmol, 63%). ¹H NMR (CDCl₃): δ 9.88 (s, 1H), 7.82 (d, J = 8.4, 2H), 6.99 (d, J = 8.4, 2H), 3.83 (d, J = 6.0, 2H), 2.05-1.04 (m, 11H).

b) **4-(Cyclohexylmethoxy)benzaldehyde semicarbazone.** The title compound was prepared in a procedure identical to that given for 4-(5-indanoxy)benzaldehyde semicarbazone in 72% yield, mp: 218-219°C. ¹H NMR (DMSO-*d*₆): δ 10.07 (s, 1H), 7.77 (s, 1H), 7.62 (d, J = 8.5, 2H), 6.92 (d, J = 8.5, 2H), 6.40 (s, 2H), 3.80 (d, J = 6.3, 2H), 1.82-1.64 (m, 6H), 1.27-1.01 (m, 5H). Anal. Calcd. for C₁₅H₂₁N₃O₂: C, 65.43; H, 7.69; N, 15.26. Found: C, 65.56; H, 7.59; N, 14.99.

Example 11**3-Fluoro-4-(4-fluorophenoxy)benzaldehyde semicarbazone**

a) **3-Fluoro-4-(4-fluorophenoxy)benzaldehyde.** A mixture of 3,4-difluorobenzaldehyde (4.9 g, 34.5 mmol), 4-fluorophenol (4.0 g, 35.7 mmol), and potassium carbonate (5.0 g, 36.2 mmol) in *N,N*-dimethylacetamide (30 mL) was refluxed for 5 h under nitrogen. After cooling, the mixture was diluted with 1:1 hexane/EtOAc (75 mL), washed with water (2 x 30 mL), 2N NaOH (20 mL), water (30 mL) and brine (20 mL), dried over Na₂SO₄, decolorized with activated charcoal, and concentrated *in vacuo* to yield the title compound as an oil (6.1 g, 26.0 mmol, 75%). ¹H NMR (CDCl₃): δ 9.89 (d, J = 2.1, 1H), 7.72-7.57 (m, 2H), 7.13-6.93 (m, 4H).

b) **3-Fluoro-4-(4-fluorophenoxy)benzaldehyde semicarbazone.** The title compound was prepared using the procedure described for 4-(5-indanoxy)benzaldehyde semicarbazone in 80% yield, mp: 233-234°C. ¹H NMR (DMSO-*d*₆): δ 10.32 (s, 1H), 7.95 (d, J = 12.6, 1H), 7.80 (s, 1H), 7.43

- 38 -

(d, $J = 9.0$, 1H), 7.27-7.21 (m, 2H), 7.11-7.05 (m, 3H), 6.54 (s, 2H). Anal Calcd. for $C_{14}H_{11}N_3O_2$: C, 57.73; H, 3.81; N, 14.43. Found: C, 57.84; H, 3.62; N, 13.81.

5

Example 12

4-(4-Tetrahydropyranoxy)benzaldehyde semicarbazone

a) **4-(4-Tetrahydropyranoxy)benzaldehyde.** A mixture of 4-hydroxybenzaldehyde (2.0 g, 16.4 mmol), 4-chlorotetrahydropyran (3.6 mL, 32.8 mmol), and potassium carbonate (4.5 g, 32.6 mmol) in *N,N*-dimethylacetamide (30 mL) was refluxed for 20 h under nitrogen. After cooling, the mixture was diluted with 1:1 hexane/EtOAc (120 mL), washed with water (2 x 30 mL), 2N NaOH (2 x 20 mL), water (30 mL) and brine (20 mL), dried over Na_2SO_4 , concentrated *in vacuo* to yield the title compound as a yellow oil (1.0 g, 4.8 mmol, 29%). 1H NMR ($CDCl_3$): δ 9.87 (s, 1H), 7.83 (d, $J = 8.5$, 2H), 7.00 (d, $J = 8.5$, 2H), 4.62 (m, 1H), 4.02-3.57 (m, 4H), 2.08-1.77 (m, 4H).

10

15

20

b) **4-(4-Tetrahydropyranoxy)benzaldehyde semicarbazone.** The title compound was prepared in a procedure identical to that given for 4-(5-indanoxy)benzaldehyde semicarbazone in 71% yield, mp: 208-209°C. 1H NMR ($DMSO-d_6$): δ 10.08 (s, 1H), 7.77 (s, 1H), 7.80 (s, 1H), 7.63 (d, $J = 8.6$, 2H), 6.98 (d, $J = 8.6$, 2H), 6.40 (s, 2H), 4.62 (p, 1H), 3.88-3.81 (m, 2H), 3.53-3.45 (m, 2H), 1.99-1.94 (m, 2H), 1.63-1.52 (m, 2H).

25

Example 13

4-(1-Methyl-4-piperidinoxy)benzaldehyde semicarbazone

a) **4-(1-Methyl-4-piperidinoxy)benzaldehyde.** A mixture of 4-hydroxybenzaldehyde (2.0 g, 16.4 mmol), 1-methyl-4-chloropiperidine hydrochloride (3.3 g, 19.4 mmol), and potassium carbonate (8.1 g, 58.6 mmol) in *N,N*-dimethylacetamide (30 mL) was refluxed for 20 h under nitrogen. After cooling, the mixture was diluted with EtOAc (120 mL), washed with water (2 x 30 mL), 2N NaOH (2 x 20 mL), water (30 mL) and brine (20 mL), dried over Na_2SO_4 , concentrated *in vacuo* to yield the title compound as a yellow oil (0.52 g, 2.4 mmol, 14%). 1H NMR ($CDCl_3$): 9.87 (s, 1H), 7.82 (d, $J = 9.0$, 2H), 6.99 (d, $J = 9.0$, 2H), 4.44 (m, 1H), 2.99 (m, 2H), 2.33-2.06 (m, 2H), 2.31 (s, 3H), 2.06-1.92 (m, 2H).

30

35

b) **4-(1-Methyl-4-piperidinoxy)benzaldehyde semicarbazone.** To a solution of 4-(4-tetrahydropyranoxy)benzaldehyde (120 mg, 0.55 mmol) in ethanol (4 mL) was added a solution of semicarbazide hydrochloride (118 mg, 1.06 mmol) and sodium acetate (90 mg, 1.1 mmol) in water (2 mL) at room temperature. After 2 h stirring, the solvent was removed in *vacuo*. To the residue was added EtOH (20 mL). The resulting solid was isolated by filtration. The filtrate was concentrated *in vacuo* to yield the product as a white solid (110 mg) which is moisture sensitive. ^1H NMR (DMSO-*d*₆): δ 10.05 (s, 1H), 7.75 (s, 1H), 7.59 (d, *J* = 8.7, 2H), 6.92 (d, *J* = 8.7, 2H), 6.37 (s, 2H), 4.83 (m, 1H), 2.61-2.54 (m, 2H), 2.18-2.12 (m, 2H), 2.15 (s, 3H), 1.92-1.85 (m, 2H), 1.64-1.58 (m, 2H).

Example 14

4-(*exo*-2-Norbornoxy)benzaldehyde semicarbazone

a) **4-(*exo*-2-Norbornoxy)benzaldehyde.** A mixture of 4-hydroxybenzaldehyde (2.1 g, 17.2 mmol), *exo*-2-bromonorbornane (4.4 mL, 34.2 mmol), and potassium carbonate (5.2 g, 37.6 mmol) in *N,N*-dimethylacetamide (30 mL) was refluxed for 5 h under nitrogen. After cooling, the mixture was diluted with 1:1 hexane/EtOAc (80 mL), washed with water (2 x 30 mL), 2N NaOH (2 x 20 mL), water (30 mL) and brine (20 mL), dried over Na₂SO₄, concentrated *in vacuo* to yield the title compound as an oil (3.3 g, 15.3 mmol, 89%). ¹H NMR (CDCl₃): δ 9.86 (s, 1H), 7.80 (d, J = 9.0, 2H), 6.96 (d, J = 9.0, 2H), 4.67 (m, 1H), 2.62-1.11 (m, 10H).

25 b) 4-(*exo*-2-Norbornoxy)benzaldehyde semicarbazone. The title compound
 was prepared in a procedure identical to that given for 4-(5-indanoxy)benzaldehyde semicarbazone in 78% yield, mp: 211-212°C.
 30 ^1H NMR (DMSO-*d*₆): δ 10.07 (s, 1H), 7.76 (s, 1H), 7.61 (d, *J* = 8.8, 2H), 6.89
 (d, *J* = 8.8, 2H), 6.40 (s, 2H), 4.69-4.66 (m, 1H), 2.54-0.95 (m, 10H).

Example 15

4-(4-Nitrophenoxy)benzaldehyde semicarbazone

a) 4-(4-Nitrophenoxy)benzaldehyde. A mixture of 4-fluorobenzaldehyde (4 mL, 37.4 mmol), 4-nitrophenol (5.2 g, 37.4 mmol), and potassium carbonate (5.3 g, 38.8 mmol) in *N,N*-dimethylacetamide (30 mL) was refluxed for 24 h

- 40 -

under nitrogen. After cooling, the mixture was diluted with 1:1 hexane/EtOAc (80 mL), washed with water (2 x 30 mL), 2N NaOH (2 x 20 mL), water (30 mL) and brine (20 mL), dried over Na_2SO_4 , concentrated *in vacuo*. The residue was purified by chromatography to yield the title compound as light yellow solid (2.1 g, 8.6 mmol, 23%). ^1H NMR (CDCl_3): δ 10.00 (s, 1H), 8.28 (d, J = 9.0, 2H), 7.96 (d, J = 8.7, 2H), 7.20 (d, J = 8.7, 2H), 7.15 (d, J = 9.0, 2H).

10 b) 4-(4-Nitrophenoxy)benzaldehyde semicarbazone. The title compound was prepared in a procedure identical to that given for 4-(5-indanoxy)benzaldehyde semicarbazone in 93% yield, mp: 221-222°C. ^1H NMR (DMSO- d_6): δ 10.28 (s, 1H), 8.27 (d, J = 9.0, 2H), 7.87 (s, 1H), 7.85 (d, J = 9.0, 2H), 7.21-7.16 (m, 4H), 6.51 (s, 2H). Anal Calcd. for $\text{C}_{14}\text{H}_{12}\text{N}_4\text{O}_4$: C, 56.00; H, 4.03; N, 18.66. Found: C, 55.96; H, 4.05; N, 18.36.

Example 16

4-(2-Fluorobenzyl)benzaldehyde semicarbazone

20 a) **4-(2-Fluorobenzyl)benzaldehyde.** A mixture of 4-hydroxybenzaldehyde (2.0 g, 16.4 mmol), 2-fluorobenzylchloride (1.9 mL, 16.0 mmol), and potassium carbonate (3.6 g, 26.0 mmol) in *N,N*-dimethylacetamide (30 mL) was refluxed for 5 h under nitrogen. After cooling, the mixture was diluted with 1:1 hexane/EtOAc (80 mL), washed with water (2 x 30 mL), 2N NaOH (2 x 20 mL), water (30 mL) and brine (20 mL), dried over Na₂SO₄, concentrated *in vacuo* to yield the title compound as a yellow solid (3.5 g, 15.2 mmol, 93%). ¹H NMR (CDCl₃): δ 9.90 (s, 1H), 7.86 (d, J = 8.7, 2H), 7.52-7.15 (m, 4H), 7.10 (d, J = 8.7, 2H), 5.22 (s, 2H).

b) 4-(2-Fluorobenzyl)benzaldehyde semicarbazone. The title compound was prepared in a procedure identical to that given for 4-(5-indanoxy)benzaldehyde semicarbazone in 86% yield, mp: 211-212°C. ¹H NMR (DMSO-*d*₆): δ 10.11 (s, 1H), 7.79 (s, 1H), 7.67 (d, *J* = 8.8, 2H), 7.59-7.54 (m, 1H), 7.48-7.40 (m, 1H), 7.29-7.22 (m, 2H), 7.05 (d, *J* = 8.8, 2H), 6.43 (s, 2H), 5.17 (s, 2H). Anal. Calcd. for C₁₅H₁₄N₃O₂: C, 62.71; H, 4.91; N, 14.63. Found: C, 62.61; H, 4.93; N, 14.51.

Example 17**4-(5,6,7,8-Tetrahydro-2-naphthoxy)benzaldehyde semicarbazone**

The title compound was prepared in a procedure identical to that given for 4-(5-indanoxy)benzaldehyde semicarbazone in 68% yield, mp: 202-204°C.

5 ^1H NMR (DMSO- d_6): δ 10.18 (s, 1H), 7.80 (s, 1H), 7.70 (d, J = 8.8, 2H), 7.09 (d, J = 8.1, 1H), 6.94 (d, J = 8.8, 2H), 6.80-6.75 (m, 2H), 6.45 (s, 2H), 2.69 (s, 4H), 1.72 (s, 4H).

Example 18**4-(2-Adamantanoxy)benzaldehyde semicarbazone**

The title compound was prepared in a procedure identical to that given for 4-(5-indanoxy)benzaldehyde semicarbazone in 58% yield, mp: 226-228°C.

10 ^1H NMR (DMSO- d_6): δ 10.08 (s, 1H), 7.77 (s, 1H), 7.62 (d, J = 8.5, 2H), 6.96 (d, J = 8.5, 2H), 6.41 (s, 2H), 4.85 (s, 1H), 4.55 (s, 1H), 2.22-1.48 (m, 13H).

15

Example 19**4-(2,4,6-Trimethylphenoxy)benzaldehyde semicarbazone**

The title compound was prepared in a procedure identical to that given for 4-(5-indanoxy)benzaldehyde semicarbazone in 66% yield, mp: 189-190°C.

20

^1H NMR (DMSO- d_6): δ 10.13 (s, 1H), 7.78 (s, 1H), 7.64 (d, J = 8.7, 2H), 6.98 (s, 2H), 2.27 (s, 3H), 2.01 (s, 6H).

Example 20**2-Fluoro-4-(4-fluorophenoxy)acetophenone semicarbazone**

25 The title compound was prepared in a procedure identical to that given for 4-(5-indanoxy)benzaldehyde semicarbazone in 75% yield, mp: 218-220°C.

^1H NMR (DMSO- d_6): δ 9.36 (s, 1H), 8.01 (d, J = 12.9, 1H), 7.62 (d, J = 9.0, 1H), 7.26-7.04 (m, 5H), 6.57 (s, 2H), 2.17 (s, 3H).

30

Example 21**4-(4-Fluorophenoxy)benzaldehyde [1-(carboxymethyl)trimethylammonium chloride]hydrazone**

To a solution of 4-(4-fluorophenoxy)benzaldehyde (337 mg, 1.56 mmol) in ethanol (10 mL) was added a solution of [1-(carboxymethyl)trimethylammonium chloride]hydrazine (263 mg, 1.57 mmol) in water (5 mL) at room temperature. The mixture was stirred at room

- 42 -

temperature for 3 days, concentrated in *in vacuo* to about 2 mL and washed with EtOAc (2 x 10 mL). The aqueous solution was concentrated to yield a white solid (228 mg, 0.59 mmol, 38%), mp: 207-209 °C. NMR indicated that product consisted of two isomers. ^1H NMR (major isomer, DMSO- d_6): δ 12.05 (s, 1H), 8.09 (s, 1H), 7.74 (d, J = 7.2, 2H), 7.31-7.12 (m, 4H), 7.05 (d, J = 7.2, 2H), 4.79 (s, 2H), 3.32 (s, 9H).

Example 22

4-(4-Fluorophenoxy)benzaldehyde carbomethoxyhydrazone

10 To a solution of 4-(4-fluorophenoxy)benzaldehyde (277 mg, 1.28 mmol) in ethanol (10 mL) was added a solution of carbomethoxyhydrazine (180 mg, 2.0 mmol) in water (5 mL), followed by AcOH (0.1 mL) at room temperature. The mixture was stirred at room temperature for 17 h and water (20 mL) was added. The resulting solid was collected by filtration, washed with water and dried in *vacuo* to yield the title compound as a white solid (228 mg, 0.74 mmol, 58%), mp: 109-111°C. ^1H NMR (DMSO- d_6): δ 11.05 (s, 1H), 8.00 (s, 1H), 7.64 (d, J = 8.7, 2H), 7.30-6.99 (m, 6H), 3.69 (s, 3H).

Example 23

20

The following semicarbazones were prepared according to the procedure described for 4-(5-indanoxy)benzaldehyde semicarbazone, starting with the necessary commercially available aldehydes:

25

Piperonal semicarbazone: mp 227-229°C; ^1H NMR (DMSO- d_6) δ 6.02 (s, 2H), 6.46 (bs, 2H), 6.88 (d, J = 7.8, 1H), 6.98-7.01 (m, 1H), 7.50 (s, 1H), 7.71 (s, 1H), 10.1 (s, 1H).

30

6-Chloropiperonal semicarbazone: ^1H NMR (DMSO- d_6) δ 6.08 (s, 2H), 6.58 (bs, 2H), 7.06 (s, 1H), 7.78 (s, 1H), 8.10 (s, 1H), 10.3 (s, 1H).

1,4-Benzodioxane-6-carboxaldehyde semicarbazone: mp 217-220°C; ^1H NMR (DMSO- d_6) δ 4.23 (s, 4H), 6.41 (bs, 2H), 6.81-6.83 (m, 1H), 7.12 (d, J = 8.4, 1H), 7.26 (s, 1H), 7.68 (s, 1H), 10.1 (s, 1H).

35

- 43 -

5 **5-Bromo-2-hydroxy-3-methoxybenzaldehyde semicarbazone:** ^1H NMR (DMSO- d_6) δ 3.80 (s, 3H), 6.51 (bs, 2H), 7.03 (d, J = 2.7, 1H), 7.67 (d, J = 2.4, 1H), 8.08 (s, 1H), 9.44 (bs, 1H), 10.3 (s, 1H).

10 **6-Methoxy-2-naphthaldehyde semicarbazone:** mp 268-289°C; ^1H NMR (DMSO- d_6) δ 3.86 (s, 3H), 6.50 (bs, 2H), 7.14-7.17 (m, 1H), 7.32 (d, J = 2.4, 1H), 7.76-7.83 (m, 2H), 7.93 (s, 2H), 8.00-8.02 (s, J = 8.4, 1H), 10.3 (s, 1H).

15 **4-Dimethylamino-1-naphthaldehyde semicarbazone:** mp 218-219°C; ^1H NMR (DMSO- d_6) δ 2.84 (s, 6H), 6.42 (s, 2H), 7.10 (d, J = 8.1, 1H), 7.50-7.61 (m, 2H), 7.89 (d, J = 7.8, 1H), 8.16-8.19 (m, 1H), 8.45 (d, J = 8.1, 1H), 8.50 (s, 1H), 10.2 (s, 1H).

20 **2-Naphthaldehyde semicarbazone:** mp 241-245°C; ^1H NMR (DMSO- d_6) δ 6.55 (bs, 2H), 7.47-7.53 (m, 2H), 7.86-7.92 (m, 3H), 7.99 (d, J = 8.4, 2H), 8.06-8.09 (m, 1H), 10.3 (s, 1H).

25 **3-Quinolinecarboxaldehyde semicarbazone:** mp 250-253°C; ^1H NMR (DMSO- d_6) δ 6.65 (bs, 2H), 7.58-7.63 (m, 1H), 7.70-7.76 (m, 1H), 7.93-8.01 (m, 3H), 8.49 (d, J = 1.5, 1H), 9.41 (d, J = 2.1, 1H), 10.5 (s, 1H).

30 **1-Methylindole-3-carboxaldehyde semicarbazone:** mp 196-199°C.

35 **2,4,6-Trimethoxybenzaldehyde semicarbazone:** mp 205-209°C.

30 **3,4,5-Trimethoxybenzaldehyde semicarbazone:** mp 210-214°C.

35 **Mesitaldehyde semicarbazone:** mp 192-195°C.

30 **2,2-Difluoro-5-formylbenzodioxole semicarbazone:** mp 219-223°C.

35 **5-Indancarboxaldehyde semicarbazone:** mp 217-220°C.

35 **Pentafluorobenzaldehyde semicarbazone:** mp 164-166°C.

- 44 -

6-Nitropiperonal semicarbazone: ^1H NMR (DMSO- d_6) δ 6.23 (s, 2H), 6.66 (bs, 2H), 7.57 (s, 1H), 7.93 (s, 1H), 8.24 (s, 1H), 10.5 (s, 1H).

5 **4-Biphenylcarboxaldehyde semicarbazone:** ^1H NMR (DMSO- d_6) δ 6.50 (bs, 2H), 7.33-7.38 (m, 1H), 7.43-7.48 (m, 2H), 7.65-7.70 (m, 4H), 7.79 (d, J = 8.4, 2H), 7.86 (s, 1H), 10.3 (s, 1H).

3,5-Dimethyl-4-hydroxybenzaldehyde semicarbazone: mp 200-205°C.

10 **Indole-3-carboxaldehyde semicarbazone:** mp 207-209°C.

Cyclohexanecarboxaldehyde semicarbazone: mp 163-168°C.

Isobutyraldehyde semicarbazone: mp 123-124°C.

15 **4-(6-Bromo-4-fluorophenoxy)benzaldehyde semicarbazone:** mp 202-205°C.

4-(N,N-Diphenylamino)benzaldehyde semicarbazone: mp 106-114°C.

20 **2-(4-Chlorophenylthio)benzaldehyde semicarbazone:** mp 206-209°C.

25 **4-Trifluoromethylbenzaldehyde semicarbazone:** ^1H NMR (DMSO- d_6) δ 6.60 (bs, 2H), 7.70 (d, J = 8.1, 2H), 7.87 (s, 1H), 7.93 (d, J = 8.1, 2H), 10.5 (s, 1H).

30 **Dibenzofuran-x-carboxaldehyde semicarbazone:** ^1H NMR (DMSO- d_6) δ 6.56 (bs, 2H), 7.42 (t, J = 7.4, 1H), 7.53 (t, J = 7.5, 1H), 7.67-7.74 (m, 2H), 7.90 (d, J = 8.4, 1H), 7.98 (s, 1H), 8.15 (d, J = 7.8, 1H), 8.52 (s, 1H), 10.3 (s, 1H).

35 **2-Fluorenecarboxaldehyde semicarbazone:** ^1H NMR (DMSO- d_6) δ 3.92 (s, 2H), 6.50 (bs, 2H), 7.29-7.40 (m, 2H), 7.58 (d, J = 6.9, 1H), 7.68 (d, J = 7.8, 1H), 7.89 (t, J = 6.6, 3H), 7.96 (s, 1H), 10.2 (s, 1H).

35 **2-Trifluoromethylbenzaldehyde semicarbazone:** mp 226-230°C.

- 45 -

3-Trifluoromethylbenzaldehyde semicarbazone: mp 206-209°C.

Diphenylacetaldehyde semicarbazone: mp 146-150°C.

5 Piperonal 2'-methylsemicarbazone: mp 224-228°C.

2,2-Difluoro-5-formylbenzodioxole 2'-methylsemicarbazone: mp 141-143°C.

10 1,4-Benzodioxane-6-carboxaldehyde 2'-methylsemicarbazone: mp 213-220°C.

6-Chloropiperonal 2'-methylsemicarbazone: mp 235-237°C.

15 6-Nitropiperonal 2'-methylsemicarbazone: mp 265-266°C.

4-Biphenylcarboxaldehyde 2'-methylsemicarbazone: mp 239-242°C.

3-Quinolinecarboxaldehyde 2'-methylsemicarbazone: mp 174-176°C.

20 2-Naphthaldehyde 2'-methylsemicarbazone: mp 204-208°C.

4-Dimethylamino-1-naphthaldehyde 2'-methylsemicarbazone: mp 163-165°C.

25 6-Methoxy-2-naphthaldehyde 2'-methylsemicarbazone: mp 212-213°C.

5-Indancarboxaldehyde 2'-methylsemicarbazone: mp 143-150°C.

30 Indole-3-carboxaldehyde 2'-methylsemicarbazone: mp 230-234°C.

1-Methylindole-3-carboxaldehyde 2'-methylsemicarbazone: mp 200-201°C.

35 4-Phenoxybenzaldehyde 2'-methylsemicarbazone: mp 162-167°C.

- 46 -

3-Phenoxybenzaldehyde 2'-methylsemicarbazone: mp 126-128°C.

Pentafluorobenzaldehyde 2'-methylsemicarbazone: mp 169-190°C.

5 **5-Bromo-2-hydroxy-3-methoxybenzaldehyde 2'-methylsemicarbazone:** mp. 177-182°C.

Mesitaldehyde 2'-methylsemicarbazone: mp 175-179°C.

10 **2,4,6-Trimethoxybenzaldehyde 2'-methylsemicarbazone:** mp 160-162°C.

3-Hydroxy-4-methoxybenzaldehyde 2'-methylsemicarbazone: mp 197-199°C.

15 **3,4-Dimethoxybenzaldehyde 2'-methylsemicarbazone:** mp 122-130°C.

3,4-Difluorobenzaldehyde 2'-methylsemicarbazone: mp 158-160°C.

4-Trifluoromethylbenzaldehyde 2'-methylsemicarbazone: mp 162-164°C.

20 **4-Trifluoromethoxybenzaldehyde 2'-methylsemicarbazone:** mp 161-163°C.

Example 24

25 **4-(4-Fluorophenoxy)benzaldehyde 2'-butylsemicarbazone**

To a solution of sodium cyanate (374 mg, 5.75 mmol) in H₂O (5mL) was added butylhydrazine oxalate (891 mg, 5.0 mmol) and H₂O (7mL). The resulting mixture was stirred at rt overnight, then concentrated to near dryness. To this residue was added 4-(4-fluorophenoxy)benzaldehyde (216 mg, 1.0 mmol), EtOH (20 mL), and H₂O (10 mL), and the mixture was further stirred at rt overnight. The precipitate was collected by vacuum filtration. Hot filtration of the precipitate in MeOH, followed by flash chromatography using 7:3 CHCl₃/EtOAc with few drops of TEA per 100 mL of the solvent mixture gave 74 mg (22 %) of the title compound as a white powder: ¹H NMR (DMSO-*d*₆) δ 0.88 (t, *J* = 7.2, 3H), 1.24-1.44 (m, 4H), 3.85 (t, *J* = 7.2, 2H),

- 47 -

6.68 (bs, 2H), 6.96 (d, J = 8.7, 2H), 7.07-7.11 (m, 2H), 7.21-7.27 (m, 2H), 7.70 (s, 1H), 7.85 (d, J = 8.4, 2H).

Example 25

4-(4-Fluorophenoxy)benzaldehyde 4'-ethylsemicarbazone

a) **4-Ethyl Semicarbazide:** A solution of ethyl isocyanate (0.45 mL, 5.74 mmol) in benzene (5 mL) was added dropwise to a stirred solution of hydrazine hydrate (0.18 mL, 5.74 mmol) in EtOH (10 mL). The resulting solution was stirred at rt for 1h. The precipitate was removed by vacuum filtration and the filtrate was concentrated to give 461 mg (78%) of the title compound as a clear liquid: ^1H NMR (CDCl_3) δ 1.10 (t, J = 7.2, 3H), 3.16-3.25 (m, 2H), 3.65 (bs, 2H), 6.04 (bs, 1H), 6.87 (s, 1H).

b) **4-(4-Fluorophenoxy)benzaldehyde 4'-ethylsemicarbazone:** A solution of 4-ethyl semicarbazide (210 mg, 2.04 mmol) and 4-(4-fluorophenoxy)benzaldehyde (435 mg, 2.01 mmol) in EtOH (20 mL) with few drops of acetic acid was stirred at rt for 1h. To the solution was added H_2O (100 mL), and the mixture was allowed to sit in an ice-bath for 30 min. The precipitate was collected by vacuum filtration, then recrystallized from EtOAC/ H_2O to afford 372 mg (61%) of the title compound as a white powder: mp 148-149°C; ^1H NMR ($\text{DMSO}-d_6$) δ 1.05 (t, J = 7.2, 3H), 3.10-3.19 (m, 2H), 6.94-6.99 (m, 3H), 7.07-7.11 (m, 2H), 7.21-7.26 (m, 2H), 7.72 (d, J = 8.4, 2H), 7.78 (s, 1H), 10.22 (s, 1H).

Example 26

4-(4-Fluorophenoxy)benzaldehyde 4',4'-dimethylsemicarbazone

a) **4,4-Dimethyl Semicarbazide:** To a stirred solution of hydrazine hydrate (441 mg, 13.8 mmol) in EtOH (20 mL) was added a solution of dimethylcarbamyl chloride (1.27 mL, 13.8 mmol) in Et_2O (10 mL) dropwise over 18 min in an ice-bath. The resulting solution was stirred in the ice-bath for 1h. The precipitate was removed by vacuum filtration and the filtrate was concentrated to give a white solid which was recrystallized from EtOAC/ CH_2Cl_2 to yield 534 mg (38%) of the title compound: ^1H NMR ($\text{DMSO}-d_6$) δ 2.81 (d, J = 18.0, 6H), 7.90 (s, 1H), 9.30 (s, 1H), 9.91 (bs, 1H).

- 48 -

b) **4-(4-Fluorophenoxy)benzaldehyde 4',4'-dimethylsemicarbazone:** A solution of 4-dimethyl semicarbazide (150 mg, 1.46 mmol) and 4-(4-fluorophenoxy)benzaldehyde (300 mg, 1.39 mmol) in EtOH (20 mL) with few drops of acetic acid was stirred at rt for 2h. To the solution was added H₂O (80 mL), and the mixture was allowed to sit in an ice-bath for 30 min. The precipitate was collected by vacuum filtration, then recrystallized from EtOAc/CHCl₃ to afford 19 mg (4.5 %) of the title compound as a white powder: mp 70-71°C; ¹H NMR (DMSO-*d*₆) δ 2.87 (s, 6H), 6.98 (d, *J* = 9.0, 2H), 7.08-7.12 (m, 2H), 7.21-7.27 (m, 2H), 7.59 (d, *J* = 8.4, 2H), 8.12 (s, 1H), 10.1 (s, 1H).

Example 27

4-(4-Fluorophenoxy)benzaldehyde 4',4'-diethylsemicarbazone

a) **4,4-Diethyl Semicarbazide:** To a stirred solution of hydrazine hydrate (432 mg, 13.5 mmol) in EtOH (20 mL) was added a solution of diethylcarbamyl chloride (1.7 mL, 13.5 mmol) in Et₂O (10 mL) dropwise over 6 min in an ice-bath. The resulting solution was stirred in the ice-bath for 1h. The precipitate was removed by vacuum filtration and the filtrate was concentrated, then triturated in Et₂O to give 592 mg (33%) of the title compound as an off white solid: ¹H NMR (DMSO-*d*₆) δ 0.98-1.06 (m, 6H), 3.15-3.27 (m, 4H), 7.81 (s, 1H), 9.30 (s, 1H), 9.91 (bs, 1H).

b) **4-(4-Fluorophenoxy)benzaldehyde 4',4'-diethylsemicarbazone:** A solution of 4-diethyl semicarbazide (191 mg, 1.46 mmol) and 4-(4-fluorophenoxy)benzaldehyde (300 mg, 1.39 mmol) in EtOH (20 mL) with few drops of acetic acid was stirred at rt for 2h. Excess 4-diethyl semicarbazide (173 mg, 1.32 mmol) was added and the resulting solution was further stirred at rt overnight. To the solution was added ice H₂O (80 mL), and the mixture was allowed to sit in an ice-bath for 30 min. The precipitate was collected by vacuum filtration, then recrystallized from EtOAc/hexane to afford 268 mg (59 %) of the title compound as a pale yellow powder: mp 69-73°C; ¹H NMR (DMSO-*d*₆) δ 1.05 (t, *J* = 7.1 Hz, 6H), 3.24-3.31 (m, 4H), 6.98 (d, *J* = 8.7 Hz, 2H), 7.08-7.13 (m, 2H), 7.21-7.27 (m, 2H), 7.58 (d, *J* = 8.7, 2H), 8.14 (s, 1H), 10.0 (s, 1H)

Example 28**4-(4-Fluorophenoxy)benzaldehyde 2'-(ethoxycarbonylmethyl)semicarbazone**

4-(4-fluorophenoxy)benzaldehyde semicarbazone (0.330 g, 2.12 mmol) was dissolved in DMF (20 mL). Sodium hydride (60% in dispersion oil, 57.5 mg, 1.44 mmol) was added to the solution. The solution was stirred at room temperature for 10 minutes, then ethyl bromoacetate (0.3 mL, 2.7 mmol) was injected. The solution was stirred for 5.5 hours, then water was added to quench the reaction. The solution was diluted with ethyl acetate, then washed with water several times to remove DMF. After evaporating off the solvent, the crude product was purified by column chromatography. The more polar product (87 mg) was identified as the title compound, mp 147-149°C. ¹H NMR (CDCl₃): δ 7.82 (d, J = 8.4 Hz, 2H), 7.55 (s, 1H), 7.24 (t, J = 8.7 Hz, 2H), 7.12-7.07 (m, 2H), 6.96 (d, J = 8.4 Hz, 2H), 6.80 (bs, 2H), 4.72 (s, 2H), 4.15-4.08 (m, 2H), 1.19 (t, J = 6.9, 3H).

15

Example 29**4-(4-Fluorophenoxy)benzaldehyde 2',4'-propylenesemicarbazone**

a) **4-(4-fluorophenoxy)benzaldehyde 2'-(3-bromopropyl)semicarbazone.** 4-(4-fluorophenoxy)benzaldehyde semicarbazone (0.35 g, 1.38 mmol) and sodium hydride (60% in dispersion oil, 57 mg, 1.42 mmol) were dissolved in DMF. After stirring for 10 minutes, 1,3-dibromopropane (2.0 mL, 19.7 mmol) was added. The solution was stirred until the yellow solution turned white or colorless. The reaction was diluted with ethylacetate/hexane (150 mL), and washed several times with water, then evaporated to dryness. The crude product was purified by column chromatography. The title product was identified by ¹H NMR (242 mg). ¹H NMR (CDCl₃): δ 7.70 (s, 1H), 7.59 (d, J = 9 Hz, 2H), 7.09-7.00 (m, 6H), 4.12 (t, J = 6.6 Hz, 2H), 3.49 (t, J = 6.0 Hz, 2H), 2.22-2.13 (m, 2H).

30

b) **4-(4-Fluorophenoxy)benzaldehyde 2',4'-propylenesemicarbazone.** The product from a) (242 mg, 0.614 mmol), and sodium hydride (60% in dispersion oil; 26 mg, 0.65 mmol) were dissolved in 25 mL of DMF at room temperature. The solution was stirred for 2 hours. The reaction was then diluted with ethyl acetate (150 mL), washed three times with water, dried over sodium sulfate, and evaporated under reduce pressure to give crude product. Purification by column chromatography gave the title compound (72 mg) mp

- 50 -

201-203°C. ^1H NMR (CDCl_3): δ 7.84 (s, 1H), 7.69 (d, J = 8.7 Hz, 2H), 7.06-6.91 (m, 6H), 6.22 (bs, 1H), 3.68 (t, J = 6 Hz, 2H), 3.35 (bs, 2H), 2.17 (t, J = 5.1 Hz, 2H).

5

Example 30

4-(4-Methylphenoxy)benzaldehyde 2'-methylsemicarbazone

a) **4-(4-methylphenoxy)benzaldehyde.** Paracresol (5mL, 47.8 mmol), potassium carbonate (7.95 g, 0.58 mol), and 4-fluorobenzaldehyde (4.3 mL, 40 mmol) in N,N-dimethylacetamide were refluxed under nitrogen for 15 hours.

10

The solution was cooled to room temperature, then diluted with hexane/ethyl acetate (1:1 ratio, 100 mL), washed with water (250 mL), aqueous sodium hydroxide (2N, 50 mL), brine (50 mL), dried over sodium sulfate, and finally evaporated under reduced pressure to give oil product (9.72 g). ^1H NMR (CDCl_3): δ 9.91 (s, 1H), 7.83 (d, J = 8.7, 2H), 7.21 (d, J = 8.1, 2H), 7.03 (d, J = 8.7, 2H), 6.98 (d, J = 8.4, 2H), 2.38 (s, 3H).

15

b) **4-(4-methylphenoxy)benzaldehyde 2'-methylsemicarbazone.** A solution of 4-(4-methylphenoxy)benzaldehyde (0.2 g) in EtOH (5 mL) was mixed with 2'-methylsemicarbazone solution (0.156 g) in 2 ml of water containing a few drops of acetic acid. After stirring for two hours, the precipitate was isolated by vacuum filtration, washed with water, and dried in vacuo to give 152 mg (57 %) of the title compound, mp: 174-176°C. ^1H NMR (CDCl_3): δ 7.58 (d, J = 8.7, 2H), 7.52 (s, 1H), 7.17 (d, J = 8.1, 2H), 6.98 (d, J = 8.7, 2H), 6.95 (d, J = 8.7, 2H), 3.36 (s, 3H), 2.35 (s, 3H).

25

Example 31

4-(4-Fluoro-2-chlorophenoxy)benzaldehyde semicarbazone

4-(4-Fluoro-2-chlorophenoxy)benzaldehyde (204 mg, 0.814 mmol), prepared as described for 4-(4-methylphenoxy)benzaldehyde, was dissolved in ethanol (5 mL). An aqueous solution of semicarbazide hydrochloride (2 mL, 1.40 mmol), and sodium acetate (1.30 mmol) were added to the solution. After stirring at rt for several hours, a precipitate formed. The mixture was filtered to isolate the solid, which after drying weighed 206 mg (82 %), mp 196-199°C. ^1H NMR ($\text{DMSO}-d_6$): δ 10.17 (s, 1H), 7.78 (s, 2H), 7.70 (d, J = 8.4 Hz, 2H), 7.66-7.62 (m, 1H), 7.28-7.25 (m, 2H), 6.89 (d, J = 8.4 Hz, 2H), 6.44 (bs, 2H).

35

The following molecules were prepared in a similar ways as described for 4-(4-methylphenoxy)benzaldehyde 2'-methylsemicarbazone or 4-(4-fluoro-2-chlorophenoxy)benzaldehyde semicarbazone.

5

4-(3,4-Methylenedioxypheoxy)benzaldehyde 2'-methylsemicarbazone, mp 197-199°C, ¹H NMR (CDCl₃): δ 7.58 (d, J = 8.4, 2H), 7.52 (s, 1H), 6.97 (d, J = 8.7, 2H), 6.79 (d, J = 8.1, 1H), 6.60 (d, J = 2.4, 1H), 6.54-6.51 (m, 1H), 6.00 (s, 2H), 3.36 (s, 3H).

10

4-(5-Indanoxy)benzaldehyde 2'-methylsemicarbazone, mp 163-165°C, ¹H NMR (CDCl₃): δ 7.58 (d, J = 8.4, 2H), 7.52 (s, 1H), 7.19 (d, J = 7.2, 1H), 6.99 (d, J = 8.7, 2H), 6.91 (s, 1H), 6.84-6.81 (m, 1H), 3.36 (s, 3H), 2.90 (t, J = 7.5, 4H), 2.16-2.08 (m, 2H).

15

4-(2-Chloro-4-fluorophenoxy)benzaldehyde 2'-methylsemicarbazone, mp 185-186°C, ¹H NMR (DMSO-d₆): δ 7.85 (d, J = 9.0, 2H), 7.67 (s, 1H), 7.64 (s, 1H), 7.28 (m, 2H), 6.93 (d, J = 8.4, 2H), 6.60 (bs, 2H), 3.22 (s, 3H).

20

4-(4-Chlorophenoxy)benzaldehyde 2'-methylsemicarbazone, mp 160-162°C, ¹H NMR (CDCl₃): δ 7.61 (d, J = 9.0, 2H), 7.53 (s, 1H), 7.32 (d, J = 8.7, 2H) 6.99 (t, J = 8.4, 4H), 3.36 (s, 3H).

25

4-(3,5-Difluorophenoxy)benzaldehyde 2'-methylsemicarbazone, mp 185-187°C, ¹H NMR (CDCl₃): δ 7.66 (d, J = 9.0, 2H), 7.55 (s, 1H), 7.08 (d, J = 9.0, 2H), 6.57-6.51 (m, 3H), 3.38 (s, 3H).

30

4-(3,4-Difluorophenoxy)benzaldehyde 2'-methylsemicarbazone, mp 170-171°C, ¹H NMR (CDCl₃): δ 7.63 (d, J = 8.7, 2H), 7.53 (s, 1H), 7.20-7.10 (m, 1H), 7.01 (d, J = 9.0, 2H), 6.91-6.84 (m, 1H), 6.80-6.81 (m, 1H), 3.37 (s, 3H).

4-(2,4-Difluorophenoxy)benzaldehyde 2'-methylsemicarbazone, mp 185-189°C, ¹H NMR (CDCl₃): δ 7.59 (d, J = 9.0, 2H), 7.52 (s, 1H), 7.16-7.08 (m, 1H), 7.01-6.89 (m, 4H), 3.36 (s, 3H).

35

4(4-Chloro-2-fluorophenoxy)benzaldehyde 2'-methylsemicarbazone, mp 170-175°C, ¹H NMR (CDCl₃): δ 7.61 (d, J = 9.0, 2H), 7.52 (s, 1H), 7.27-7.02 (m, 3H), 6.98 (d, J = 8.7, 2H), 3.36 (s, 3H).

5 5,6,7,8-Tetrahydro-2-naphthoxybenzaldehyde 2'-methylsemicarbazone, mp 120-124°C, ¹H NMR (CDCl₃): δ 7.58 (d, J = 8.4, 2H), 7.52 (s, 1H), 7.07-6.97 (m, 3H), 6.81-6.76 (m, 2H), 3.36 (s, 3H).

10 4-(4-Fluorophenoxy)-3-fluorobenzaldehyde 2'-methylsemicarbazone, mp 169-172°C, ¹H NMR (CDCl₃): δ 7.50 (d, J = 11, 1H), 7.47 (s, 1H), 7.29 (d, J = 8.4 1H), 7.08-6.95 (m, 5H), 3.36 (s, 3H).

15 2-(4-Fluorophenoxy)-4-fluorobenzaldehyde 2'-methylsemicarbazone, mp 173-175°C, ¹H NMR (CDCl₃): δ 7.90 (d, J = 7.8, 1H), 7.87 (s, 1H), 7.30 (d, J = 8.1, 1H), 7.14 (t, J = 7.5, 1H), 7.08-6.94 (m, 4H), 6.83 (d, J = 8.4, 1H), 3.31 (s, 3H).

20 4-(4-Fluorophenoxy)-2-fluorobenzaldehyde 2'-methylsemicarbazone, mp 122-125°C.

25 2,6-Difluoro-4-(4-fluorophenoxy)benzaldehyde 2'-methylsemicarbazone, mp 135-136°C, ¹H NMR (CDCl₃): δ 7.67 (s, 1H), 7.09-7.00 (m, 6H), 3.29 (s, 3H).

30 4-(2,4,6-Trimethylphenoxy)benzaldehyde 2'-methylsemicarbazone, mp 165-167°C, ¹H NMR (CDCl₃): δ 7.54 (s, 1H), 7.51 (d, J = 4.2, 2H), 6.91 (s, 2H), 6.78 (d, J = 8.7, 2H), 3.34 (s, 3H), 2.31 (s, 3H), 2.08 (s, 6H).

35 4-(3,4-Methylenedioxyphenoxy)-3-fluorobenzaldehyde 2'-methylsemicarbazone, mp 149-151°C, ¹H NMR (CDCl₃): δ 7.50 (d, J = 9.9, 1H), 7.47 (s, 1H), 6.95 (t, J = 8.7, 1H), 6.76 (d, J = 8.4, 1H), 6.60 (d, J = 2.4, 1H), 6.51-6.48 (m, 1H), 5.99 (s, 2H), 3.35 (s, 3H).

3-Fluoro-4-(5-indanoxy)benzaldehyde 2'-methylsemicarbazone, mp 140-145°C, ¹H NMR (CDCl₃): δ 7.52-7.45 (m, 2H), 7.28-7.28 (m, 1H), 7.18 (d, J = 8.7, 2H), 3.36 (s, 3H).

= 8.4, 1H), 6.98 (t, J = 10.2, 1H), 6.88 (s, 1H), 6.81 (d, J = 9.9, 1H), 3.36 (s, 3H), 2.89 (t, J = 7.5, 4H), 2.13-2.08 (m, 2H).

5 **3-Chloro-4-(4-fluorophenoxy)benzaldehyde 2'-methylsemicarbazone**, mp 203-204°C, ¹H NMR (CDCl₃): δ 7.77 (d, J = 2.1, 1H), 7.45 (s, 1H), 7.42 (d, J = 8.4, 1H), 7.09-6.96 (m, 4H), 6.89 (d, J = 8.4, 1H), 3.36 (s, 3H).

10 **3-Chloro-4-(4-fluorophenoxy)benzaldehyde 2'-methylsemicarbazone**, mp 147-150°C, ¹H NMR (CDCl₃): δ 7.85 (s, 1H), 7.82 (d, J = 2.7, 1H), 7.08-6.95 (m, 4H), 6.67 (d, J = 9.0, 1H), 6.43 (d, J = 2.7, 1H), 3.30 (s, 3H).

15 **4-(4-Fluorophenoxy)-2-Trifluoromethylbenzaldehyde 2'-methylsemicarbazone**, mp, ¹H NMR (CDCl₃): δ 7.98 (d, J = 9.3, 1H), 7.78 (s, 1H), 7.13-7.02 (m, 6H), 3.37 (s, 3H).

20 **3-Chloro-4-(4-fluorophenoxy)benzaldehyde semicarbazone**, mp 204-208°C, ¹H NMR (DMSO-d₆): δ 10.3 (s, 1H), 8.09 (d, J = 1.8, 1H), 7.78 (s, 1H), 7.57 (d, J = 8.7, 1H), 7.28 (t, J = 9.0, 2H), 7.07-7.02 (m, 2H), 6.97 (d, J = 8.7, 1H), 6.65 (bs, 2H).

25 **2-Chloro-4-(4-fluorophenoxy)benzaldehyde semicarbazone**, mp 210-213°C, ¹H NMR (DMSO-d₆): δ 10.20 (s, 1H), 8.13 (d, J = 9.0, 1H), 8.07 (s, 1H), 7.12-7.04 (m, 4H), 6.73 (d, J = 8.1, 1H), 6.45 (bs, 2H), 6.35 (s, 1H).

30 **4-(4-Fluorophenoxy)-2-Trifluoromethylbenzaldehyde semicarbazone**, mp 182-185°C, ¹H NMR (DMSO-d₆): δ 10.48 (s, 1H), 8.40 (d, J = 9.3, 1H), 7.29-7.20 (m, 6H), 6.57 (bs, 2H).

35 **2-(4-Fluorophenoxy)-4-fluorobenzaldehyde semicarbazone**, mp 176-180°C, ¹H NMR (DMSO-d₆): δ 9.23 (s, 1H), 7.56 (d, J = 8.7, 1H), 7.24-7.00 (m, 5H), 6.70 (d, J = 8.4, 1H), 6.42 (d, J = 2.4, 1H), 6.24 (bs, 2H).

40 **4-(2-Chloro-4-fluorophenoxy)benzaldehyde semicarbazone**, mp 196-199°C, ¹H NMR (DMSO-d₆): δ 10.17 (s, 1H), 7.78 (s, 1H), 7.70 (d, J = 8.4, 2H), 7.63 (d, J = 7.5, 1H), 7.26 (d, J = 6.3, 2H), 6.89 (d, J = 8.4, 2H), 6.44 (bs, 2H).

4-(4-Chlorophenoxy)benzaldehyde semicarbazone, mp 219-221°C, ¹H NMR (DMSO-*d*₆): δ 10.19 (s, 1H), 7.80 (s, 1H), 7.73 (d, J = 9.0, 2H), 7.43 (d, J = 9.0, 2H), 7.05 (d, J = 8.7, 2H), 7.00 (d, J = 9.0, 2H), 6.45 (bs, 2H).

5 4-(3,5-Difluorophenoxy)benzaldehyde semicarbazone, mp 186-191°C, ¹H NMR (DMSO-*d*₆): δ 10.23 (s, 1H), 7.82 (s, 1H), 7.77 (d, J = 8.4, 2H), 7.10 (d, J = 8.1, 2H), 7.06-6.96 (m, 1H), 6.76 (d, J = 6.6, 2H), 6.47 (bs, 2H).

10 4-(2,4-Difluorophenoxy)benzaldehyde semicarbazone, mp 220-223°C, ¹H NMR (DMSO-*d*₆): δ 10.17 (s, 1H), 7.78 (s, 1H), 7.69 (d, J = 8.7, 2H), 7.49 (m, 1H), 7.33 (m, 1H), 7.14 (m, 1H), 6.93 (d, J = 8.1, 2H), 6.43 (bs, 2H).

15 4-(2-Fluoro-4-chlorophenoxy)benzaldehyde semicarbazone, mp 218-220°C, ¹H NMR (DMSO-*d*₆): δ 10.19 (s, 1H), 7.79 (s, 1H), 7.37-7.63 (m, 3H), 7.30-7.23 (m, 2H), 6.98 (d, J = 7.8, 2H), 6.44 (bs, 2H).

20 2-Fluoro-4-(4-fluorophenoxy)benzaldehyde semicarbazone, mp 217-219°C, ¹H NMR (DMSO-*d*₆): δ 10.21 (s, 1H), 8.13 (d, J = 8.4, 1H), 8.07 (s, 1H), 7.24-7.18 (m, 4H), 6.74 (d, J = 9.6, 1H), 6.45 (bs, 2H), 6.36 (s, 1H).

Example 32

4-(3-Octoxy)benzaldehyde semicarbazone and 4-(3-Octoxy)benzaldehyde 2'-methylsemicarbazone

a) 4-(3-octoxy)benzaldehyde. A solution of 3-bromooctane (792 mg, 0.41 mmol), 4-hydroxylbenzaldehyde (948 mg, 0.776 mmol), and potassium carbonate in N,N-dimethylacetamide (30 mL) were refluxed for 17 hours. The reaction was allowed to cool to rt, then diluted with hexane/ethylacetate (1:1 ratio, 100 mL), washed with water (80 mL), aqueous sodium hydroxide (2N, 100 mL), brine (100 mL), dried over sodium sulfate, and finally concentrated under reduce pressure to give a yellow liquid (0.33 g, 34% yield). ¹H NMR (CDCl₃): δ 4.1-3.9 (m, 1H), 1.95-1.20 (m, 10H), 1.00-0.81 (m, 6H).

b) 4-(3-Octoxy)benzaldehyde semicarbazone. This molecule was prepared as described for 4-(4-fluoro-2-chlorophenoxy)benzaldehyde semicarbazone, mp 45°C, ¹H NMR (DMSO-*d*₆): δ 10.05 (s, 1H), 7.74 (s, 1H), 7.59 (d, J = 8.1,

- 55 -

2H), 6.89 (d, J = 8.7, 2H), 6.38 (bs, 2H), 4.32-4.28 (m, 1H), 1.59-1.52, 1.24-1.19, 0.90-0.82 (m, 16H).

5 **c) 4-(3-Octoxy)benzaldehyde 2'-methylsemicarbazone.** This molecule was prepared as described for 4-(4-methylphenoxy)benzaldehyde 2'-methylsemicarbazone, mp 45°C, ¹H NMR (DMSO-*d*₆): δ 7.72 (d, J = 8.7, 2H), 7.60 (s, 1H), 6.91 (d, J = 9.0, 2H), 6.68 (bs, 2H), 4.32-4.29 (m, 1H), 3.19 (s, 3H), 1.60-1.57 (m, 4H), 1.26 (bs, 7H), 0.91-0.83 (m, 5H).

10 The following molecules were synthesized as described for 4-(3-octoxy)benzaldehyde semicarbazone or 4-(3-octoxy)benzaldehyde 2'-methylsemicarbazone:

15 **4-Cycloheptoxybenzaldehyde 2'-methylsemicarbazone**, mp 165-169°C. ¹H NMR (CDCl₃): δ 7.55 (d, J = 9.0, 2H), 7.50 (s, 1H), 6.88 (d, J = 9.0, 2H), 4.45 (m, 1H), 3.35 (s, 3H), 2.03-2.00 (m, 4H), 1.82-1.77 (m, 4H), 1.49 (m, 4H)

4-(4-Nitrophenoxy)benzaldehyde 2'-methylsemicarbazone, mp 180-185°C.

20 **4-Adamantanoxybenzaldehyde 2'-methylsemicarbazone**, 162°C. ¹H NMR (CDCl₃): δ 7.55 (d, J = 9.0, 2H), 7.51 (s, 1H), 6.94 (d, J = 8.7, 2H), 4.46 (s, 1H), 3.35 (s, 3H), 2.17, 1.90, 1.76 (bs, 12H).

25 **4-(Diphenylmethoxy)benzaldehyde 2'-methylsemicarbazone**, 141-145°C, mp 141-145°C, ¹H NMR (CDCl₃): δ 7.51-7.26 (m, 13) 6.97 (d, J = 9.0, 2H), 6.25 (s, 2H), 3.32 (s, 3H).

30 **4-Triphenylmethoxybenzaldehyde semicarbazone**, 139-142°C, ¹H NMR (DMSO-*d*₆): δ 10.04 (s, 1H), 7.63 (s, 1H), 7.42-7.18 (m, 17 H), 6.64 (d, J = 9.0, 2H), 6.35 (bs, 2H).

35 **4-(Diphenylmethoxy)benzaldehyde semicarbazone**, 128°C. ¹H NMR (DMSO-*d*₆): δ 10.06 (s, 1H), 7.70 (s, 1H), 7.56 (d, J = 9.0, 2H), 7.48 (d, J = 8.1, 4H), 7.36-7.24 (m, 4H), 7.18 (d, J = 5.7, 2H), 7.00 (d, J = 3.5, 2H), 6.57 (s, 1H), 6.37 (bs, 2H).

- 56 -

4-(exo-2-Norbornoxy)benzaldehyde 2'-methylsemicarbazone, 180-185°C.

¹H NMR (CDCl₃): δ 7.54 (d, J = 8.4, 2H), 7.50 (s, 1H), 6.88 (d, J = 8.4, 2H), 4.60 (m, 1H), 2.6-1.2 (m, 10H).

5

4-(4-Tetrahydropyranoxy)benzaldehyde 2'-methylsemicarbazone, mp 185-186°C. ¹H NMR (CDCl₃): δ 7.57 (d, J = 8.4, 2H), 7.51 (s, 1H), 6.94 (d, J = 9.0, 2H), 4.54 (m, 1H), 4.03-3.60 (m, 2H), 3.63-3.35 (m, 2H), 3.35 (s, 3H), 2.02 (m, 2H), 1.82 (m, 2H).

10

Example 33

4-Benzylbenzaldehyde semicarbazone and 4-Benzylbenzaldehyde 2'-methylsemicarbazone

15

a) **4-Benzylbenzaldehyde.** A solution of (4-bromophenyl)phenylmethane (5.42 mmol) in 30 mL of dry THF at -78°C was treated with *n*BuLi (4.4 mL of 1.6M in hexane). After 1 h, *N*-formylpiperidine (5.94 mmol in THF) was added via syringe. The solution was stirred overnight and then evaporated under reduced pressure. Column chromatography gave the title product (1.74 g). ¹H NMR (CDCl₃): δ 9.55 (s, 1H), 7.84 (d, 2H), 7.45-7.15 (m, 6H), 4.10 (s, 2H). ¹H NMR (CDCl₃): δ 9.55 (s, 1H), 7.84 (d, 2H), 7.45-7.15 (m, 6H), 4.10 (s, 2H).

20

b) **4-Benzylbenzaldehyde semicarbazone** was prepared as described for 4-(4-fluoro-2-chlorophenoxy)benzaldehyde semicarbazone, mp 118-120°C. ¹H NMR (DMSO-*d*₆): δ 10.12 (s, 1H), 7.78 (s, 1H), 7.60 (d, J = 7.5, 2H), 7.30-7.17 (m, 6H), 6.37 (bs, 2H), 3.94 (s, 2H).

25

c) **4-Benzylbenzaldehyde 2'-methylsemicarbazone** was prepared as described for 4-(4-methylphenoxy)benzaldehyde 2'-methylsemicarbazone, mp 142-144°C. ¹H NMR (CDCl₃): δ 7.56 (d, J = 8.1, 2H), 7.30-7.12 (m, 6H), 4.00 (s, 2H), 3.35 (s, 3H).

30

Example 34

4-(4-Trifluoromethylphenoxy)benzaldehyde 2'-methylsemicarbazone and 4-(4-Trifluoromethylphenoxy)benzaldehyde semicarbazone

35

a) **4-(4-Trifluoromethylphenoxy)benzaldehyde.** Trifluoro-*p*-cresol (1.608 g, 0.992 mmol) was dissolved in anhydrous THF (20 mL) at 0°C. The

solution was purged with nitrogen for 10 minutes. Sodium hydride (60% in dispersion oil, 0.522 g, 13.0 mmol) was added to the solution. The solution was stirred at 0°C for 50 minutes, then the ice bath was removed. 4-Fluorobenzaldehyde was then added (0.925 mL, 8.60 mmol). The solution was stirred overnight. The solution was diluted with hexane/ethylacetate (1:1 ratio, 60 mL), washed with water, aqueous sodium hydroxide (2 N, 50 mL), brine, and dried over sodium sulfate. The organic layer was evaporated under reduced pressure to give solid product (0.570 g, 22% yield).

10 b) **4-(4-Trifluoromethylphenoxy)benzaldehyde 2'-methylsemicarbazone.** The title compound was prepared as described for 4-(4-methylphenoxy)benzaldehyde 2'-methylsemicarbazone, mp 156-159°C, ¹H NMR (CDCl₃): δ 7.65-7.60 (m, 4H), 1.52 (s, 1H), 7.09 (t, J = 8.4, 2H), 3.36 (s, 3H).

15 c) **4-(4-Trifluoromethylphenoxy)benzaldehyde semicarbazone.** The title compound was prepared as described for 4-(4-fluoro-2-chlorophenoxy)benzaldehyde semicarbazone, mp 119-122°C, ¹H NMR (DMSO-d₆): δ 10.21 (s, 1H), 7.80-7.74 (m, 5H), 7.20 (t, J = 7.8, 4H), 6.48 (bs, 2H).

Example 35

4-(4-Fluorophenoxy)benzaldehyde 2'-(carbamylmethyl)semicarbazone

25 4-(4-Fluorophenoxy)benzaldehyde semicarbazone (0.674 g, 2.47 mmol) and sodium hydride (60% in dispersion oil, 104 mg, 2.60 mmol) were added to DMF (30 mL) giving a yellow solution. After 10 min, 2-bromoacetamide (0.693 g, 5.00 mmol) was added. When the reaction had decolorized, ethyl acetate (150 mL) was added and the reaction was washed with water (3 x). The organic layer was separated and concentrated to give a solid. The crude product was purified by column chromatography to give 100 mg (12%) of the title compound, mp 219-223°C. ¹H NMR (DMSO-d₆): δ 7.79 (d, J=7.5, 2H), 7.45 (s, 2H), 7.24 (t, J = 8.1, 2H), 7.113 (m, 2H), 6.95 (d, J = 8.1, 2H), 4.49 (s, 2H).

The following compounds were prepared similarly:

5 **4-(4-Fluorophenoxy)benzaldehyde 2'-(3-cyanopropyl)semicarbazone**, mp 167-178°C. ¹H NMR (CDCl₃): δ 7.59 (d, J = 9.6, 3H), 7.06-6.96 (m, 6H), 4.11 (t, J = 6.6, 2H), 2.46 (t, J = 7.2, 2H), 2.04-1.96 (m, 2H).

10 **4-(4-Fluorophenoxy)benzaldehyde 2'-(2-propynyl)semicarbazone**, mp 141-142°C. ¹H NMR (DMSO-d₆): δ 7.86 (d, J = 8.7, 2H), 7.76 (s, 1H), 7.24 (t, J = 9.0, 2H), 7.12-7.08 (m, 4H), 6.97 (d, J = 8.7, 2H), 6.80 (bs, 2H) 4.72 (s, 2H).

15 **4-(4-Fluorophenoxy)benzaldehyde 2'-(2-ethoxycarbonylmethyl)semicarbazone**: mp 147-149°C, ¹H NMR (DMSO-d₆): δ 7.82 (d, J = 8.4, 2H), 7.55 (s, 1H), 7.24 (t, J = 8.7, 2H), 7.12-7.07 (m, 2H), 6.96 (d, J = 8.4, 2H), 6.80 (bs, 2H), 4.72 (s, 2H), 4.15-4.08 (m, 2H), 1.19 (t, J = 6.9, 3H).

20 **4-(4-Fluorophenoxy)benzaldehyde 2'-(2-propenyl)semicarbazone**, mp 134-135°C. ¹H NMR (DMSO): δ 7.80 (d, J = 8.7, 2H), 7.56 (s, 1H), 7.23 (t, J = 8.7, 2H), 7.10-7.06 (m, 2H), 6.94 (d, J = 8.4, 2H), 6.69 (bs, 2H), 5.78-5.74 (m, 1H), 5.10 (d, J = 10.2, 1H), 4.99 (d, J = 17.1, 1H), 4.53 (s, 2H).

25 **4-(4-Fluorophenoxy)benzaldehyde 2'-benzylsemicarbazone**: mp 182-183°C. ¹H NMR (DMSO): δ 7.72 (d, J = 7.8, 2H), 7.56 (s, 1H), 7.31 (t, J = 7.2, 3H), 7.22 (m, 4H), 7.08-7.05 (m, 2H), 6.90 (d, J = 7.2, 2H), 5.15 (s, 2H).

Example 36

4-(4-Fluorophenoxy)benzaldehyde semicarbazone as Na⁺ channel blocker

4-(4-Fluorophenoxy)benzaldehyde semicarbazone was tested in the electrophysiological and binding assays described above and produced dose-dependent inhibition of voltage-gated Na⁺ currents recorded in acutely dissociated rat hippocampal neurons. The blocking effect of this compound on Na⁺ currents was highly sensitive to the holding voltage. For example, at concentrations between 0.1 - 10 μ M, 4-(4-fluorophenoxy)benzaldehyde semicarbazone had very little effect on Na⁺ currents activated from a holding membrane voltage of -100 mV, but inhibited currents with increasing potency as the holding potential was progressively depolarized.

Table 1 presents the IC_{50} values derived from concentration-inhibition curves for the captioned compound taken at different holding voltages. The most potent block in these studies was seen at a membrane holding voltage of -60 mV. At this holding voltage the Na^+ current was decreased by 65% as compared to currents elicited from a holding voltage of -100 mV. The decrease in current was due to steady-state inactivation of the Na^+ channels. There was a direct correlation between inhibitory potency of the captioned compound and the degree of Na^+ channel inactivation (Table 1): the higher the degree of inactivation the higher the potency of antagonism. 4-(4-Fluorophenoxy)benzaldehyde semicarbazone appeared to have little effect on the overall shape of the Na^+ channel current-voltage relationship measured at peak current.

This data indicates that 4-(4-fluorophenoxy)benzaldehyde semicarbazone binds to voltage-sensitive Na^+ channels in their inactivated states and has weak potency towards Na^+ channels in their resting states (Ragsdale *et al.*, *Mol. Pharmacol.* 40:756-765 (1991); Kuo and Bean, *Mol. Pharmacol.* 46:716-725 (1994)). The apparent antagonist dissociation constant (K_d) of this compound for inactivated Na^+ channels is ~0.6 μ M.

Table 1. Relationship between holding potential, potency of Na^+ current inhibition by 4-(4-fluorophenoxy)benzaldehyde semicarbazone, and level of Na^+ current inactivation.

HOLDING POTENTIAL (mV)	IC_{50} (μ M)	Na^+ CURRENT INACTIVATION %
-100	>30	0
-90	25	2
-80	4.9	8
-70	2.2	25
-60	1	65

- 60 -

Table 2. Modulation of site 1 and site 2 of Na^+ channel by 4-(4-fluorophenoxy)benzaldehyde semicarbazone (Compound A).

Na^+ CHANNEL	COMPOUND	IC_{50}
Site 1	Tetrodotoxin	12 nM
	Lidocaine	>100 μM
	Compound A	>100 μM
Site 2	Tetrodotoxin	>100 μM
	Lidocaine	29.9 μM
	Compound A	22 μM

5

Example 37

Antinociceptive activity of 4-(4-Fluorophenoxy)benzaldehyde semicarbazone

Analgesic activity of 4-(4-fluorophenoxy)benzaldehyde semicarbazone was assessed in the formalin test. The method of Hunskaar, *et al.*, *J. Neurosci. Method* 14:69-76 (1985), was used with some modifications as described in 10 the following.

Mice were placed in Plexiglas jars for at least 1 h to accommodate to experimental conditions. Following the accommodation period, mice were weighed and injected with 4-(4-Fluorophenoxy)benzaldehyde semicarbazone by i.p. or p.o. administration. Control mice were injected with saline (10 ml/kg). Fifteen min (i.p.) or 30 min (p.o.) following 4-(4-fluorophenoxy)benzaldehyde semicarbazone administration mice were injected with formalin (20 ml of 5% formaldehyde solution in saline) into the dorsal surface of the right hand paw. Mice were immediately transferred to the Plexiglas jars and the amount of time that each mouse spent licking and/or biting the injected paw was recorded for every 5-min period over the 1 h observation period. The data presented here are at 0-5 min (early phase) and from 5-60 min (late phase) following formalin injections. The late phase of 15 the formalin test is the average of eleven 5-min periods.

20

The result of this test are shown in Figure 1. The antinociceptive activity of 4-(4-fluorophenoxy)benzaldehyde semicarbazone is demonstrated. The compound has a potency of ED_{50} about 5-10 mg/kg by both routes of administration.

5

Example 38

4-(3,4-Methylenedioxypheoxy)benzaldehyde semicarbazone as anticonvulsant

10 The ability of 4-(3,4-methylenedioxypheoxy)benzaldehyde semicarbazone to block maximal electroshock-induced seizures (MES) was determined by the following procedure.

15 Seizures were induced by application of current (50 mA, 60 pulses/sec, 0.8 msec pulse width, 1 sec duration, D.C.) using a Ugo Basile ECT device (model 7801). Mice were restrained by gripping the loose skin on their dorsal surface and saline-coated corneal electrodes were held lightly against the two cornea. Current was applied and mice were observed for a period of up to 30 sec for the occurrence of a tonic hindlimb extensor response. A tonic seizure was defined as a hindlimb extension in excess of 90 degrees from plane of the body.

20 4-(3,4-Methylenedioxypheoxy)benzaldehyde semicarbazone was administered orally to mice 30 min before the test procedure. The compound exhibited protection against MES with an ED_{50} (the dose provided protection of 50% of animals) of 5.3 mg/kg.

25 Additional compounds of the present invention were further tested in vitro and in vivo and the results are presented in Table 3. The relative in vitro potency of these compounds were determined by their ability to inhibit human skeletal muscle Na^+ channel subunit stable expressed in HEK-293 cells. The techniques employed for Na^+ current recordings and analysis with the use of this cell line were similar to that described in example 36. These studies employ depolarizing prepulses of varying duration to allow drugs to bind, a brief (5 ms) repolarizing step to reprime unbound channels, followed by the test pulse (5 ms) to measure what proportion of channels are inhibited. The reduction in peak currents is then plotted as a function of prepulse duration and the time constant (τ) measured by monoexponential fit. A plot of $1/\tau$ as a function of antagonist concentration then allows the macroscopic binding rates of the antagonists to be calculated. The anticonvulsant activities of additional

compounds of the present invention were determined as described in example 38.

Table 3.

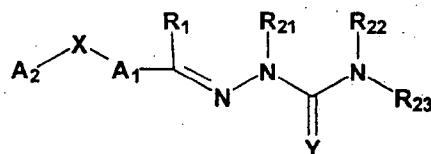
Compound Name	HsmNa ⁺ Ki ((M))	MES (ED ₅₀ mg/kg)
4-(2-pyrimidinoxy)benzaldehyde semicarbazone	1.1	
4-cycloheptoxybenzaldehyde semicarbazone	0.25	3.2
4-(5-indanoxy)benzaldehyde semicarbazone	0.04	1.7
3-fluoro-4-(4-fluorophenyl)benzaldehyde semicarbazone	0.68	3
4-(4-fluorophenoxy)benzaldehyde semicarbazone	0.21	1.6
4-(4-butoxyphenoxy)benzaldehyde semicarbazone	6	14.9
4-(3,4-methylenedioxyphenoxy)benzaldehyde semicarbazone	0.67	3.4
3-[4-(4-Fluorophenoxy)phenyl]methylene]aminooxazolidin-2-one	67	
4-(4-fluorophenyl)benzoylsemicarbazide	70	
4-(3,4-difluorophenoxy)benzaldehyde semicarbazone	0.2	
4-(2-fluoro-4-chlorophenoxy)benzaldehyde semicarbazone	0.06	
4-(4-fluorothiophenoxy)benzaldehyde semicarbazone	0.13	
lamotrigine	16	

Compound Name	HsmNa ⁺ Ki ((M)	MES (ED ₅₀ mg/kg)
4-(4-fluorophenyl)benzaldehyde 2'-methylsemicarbazone	0.15	1.5
2-[4-(3-fluorobenzyl)oxy]benzylamino]-2'-methylpropanamide	0.4	
4-(4-fluorophenoxy)phenylmethylsemicbazide	7.5	4.2
4-(4-fluorophenoxy)-3-fluorobenzaldehyde 2'-methylsemicarbazone	0.15	0.9
2'-methyl-4-(4-fluorophenoxy)phenylmethylsemicbazide	16	3.2

Having now fully described this invention, it will be understood by those of ordinary skill in the art that the same can be performed within a wide and equivalent range of conditions, formulations and other parameters without affecting the scope of the invention or any embodiment thereof. All patents and publications cited herein are fully incorporated by reference herein in their entirety.

What Is Claimed Is:

1. A method of treating a disorder responsive to the blockade of sodium channels in a mammal suffering therefrom, comprising administering to a mammal in need of such treatment an effective amount of a compound having the Formula I:



I

10 or a pharmaceutically acceptable salt or prodrug thereof, wherein:
 Y is oxygen or sulfur;
 R₁ is hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl;
 R₂₁, R₂₂ and R₂₃ are independently hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl, or R₂₁ is defined as above, and R₂₂ and R₂₃ together with the nitrogen atom to which they are attached form a heterocycle selected from the group consisting of piperidine, piperazine and morpholine;
 15 A₁ and A₂ are independently aryl, heteroaryl, saturated or partially unsaturated carbocycle or saturated or partially unsaturated heterocycle, any of which is optionally substituted;
 20 A₁ and A₂ are independently aryl, heteroaryl, saturated or partially unsaturated carbocycle or saturated or partially unsaturated heterocycle, any of which is optionally substituted;
 X is one or O, S, NR₂₄, CR₂₅R₂₆, C(O), NR₂₄C(O), C(O)NR₂₄, SO, SO₂ or a covalent bond; where
 25 R₂₄ is hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl; and
 R₂₅ and R₂₆ are independently hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl;
 provided when both Ar₁ and Ar₂ are phenyl and X is O or S, then said disorder is other than convulsions.

2. The method according to claim 1, wherein A₁ and A₂ are both optionally substituted aryl moieties.

3. The method according to claim 1, wherein
5 A₁ and A₂ are phenyl moieties, that are each independently optionally substituted by one or two substituents independently selected from the group consisting of halogen, C₁₋₆ alkyl, C₃₋₈ cycloalkyl, cyano, C₁₋₆ alkoxy and C₆₋₁₀ aryloxy;

Y is O;
10 R₁ is hydrogen, C₁₋₆ alkyl, C₃₋₈ cycloalkyl or C₆₋₁₀ aryl;
R₂₁, R₂₂ and R₂₃ are independently hydrogen or C₁₋₆ alkyl; and
X is oxygen or sulfur.

4. The method according to claim 1, wherein at least one of R₂₁,
15 R₂₂ and R₂₃ is C₁₋₆ alkyl.

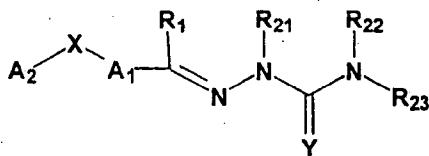
5. The method according to claim 1, wherein said compound is selected from the group consisting of:
4-phenoxybenzaldehyde semicarbazone;
20 4-(3,4-methylenedioxyphenoxy)benzaldehyde semicarbazone;
4-(4-fluorophenoxy)benzaldehyde semicarbazone;
4-(4-chlorophenoxy)benzaldehyde semicarbazone;
4-(4-bromophenoxy)benzaldehyde semicarbazone;
4-(4-methoxyphenoxy)benzaldehyde semicarbazone;
25 4-(4-trifluoromethylphenoxy)benzaldehyde semicarbazone;
4-(4-methylphenoxy)benzaldehyde semicarbazone;
4-(3,4-difluorophenoxy)benzaldehyde semicarbazone;
4-(4-chloro-2-fluorophenoxy)benzaldehyde semicarbazone;
4-(4-nitrophenoxy)benzaldehyde semicarbazone;
30 4-(3-methylphenoxy)benzaldehyde semicarbazone;
4-(4-*t*-butylphenoxy)benzaldehyde semicarbazone;
4-(4-propylphenoxy)benzaldehyde semicarbazone;
4-(4-*s*-butylphenoxy)benzaldehyde semicarbazone;
4-(4-bromophenoxy)acetophenone semicarbazone;
35 4-(4-fluorophenoxy)acetophenone semicarbazone;
4-(4-fluorophenoxy)-3-fluoroacetophenone semicarbazone;

4-(4-chlorophenoxy)acetophenone semicarbazone;
4-(4-bromophenoxy)propiophenone semicarbazone;
4-(4-fluorophenoxy)propiophenone semicarbazone;
4-(4-chlorophenoxy)propiophenone semicarbazone;
5 4-phenylmercaptopbenzaldehyde semicarbazone;
4-(4-fluorophenylmercapto)benzaldehyde semicarbazone;
4-(4-chlorophenylmercapto)benzaldehyde semicarbazone;
4-cyclohexyloxybenzaldehyde semicarbazone;
4-cycloheptyloxybenzaldehyde semicarbazone;
10 4-(5-indanyloxy)benzaldehyde semicarbazone;
4-(6-quinolinylloxy)benzaldehyde semicarbazone;
4-(4-fluorophenoxy)-3-fluorobenzaldehyde semicarbazone;
4-(4-fluorophenoxy)cyclohexane-1-carboxaldehyde semicarbazone;
4-(tetrahydropyranloxy)benzaldehyde semicarbazone;
15 4-(1-methyl-4-piperidinoxy)benzaldehyde semicarbazone;
4-(diphenylmethoxy)benzaldehyde semicarbazone;
4-(4-trifluoromethylphenoxy)benzaldehyde 2'-methylsemicarbazone;
4-(diphenylmethoxy)benzaldehyde 2'-methylsemicarbazone;
4-benzylbenzaldehyde 2'-methylsemicarbazone;
20 4-(5-indanyloxy)benzaldehyde 2'-methylsemicarbazone;
4-(3,4-methylenedioxyphenoxy)benzaldehyde 2'-methylsemicarbazone;
3-fluoro-4-(3,4-methylenedioxyphenoxy)benzaldehyde
2'-methylsemicarbazone;
4-(4-nitrophenoxy)benzaldehyde 2'-methylsemicarbazone;
25 4-(4-fluorophenoxy)-3-fluorobenzaldehyde 2'-methylsemicarbazone;
4-(4-fluorophenoxy)benzaldehyde 4'-methylsemicarbazone; and
4-(4-fluorophenoxy)benzaldehyde 2'-methylsemicarbazone.

6. The method according to claim 1, wherein said compound is
30 selected from the group consisting of:
4-(2-pyridinoxy)benzaldehyde semicarbazone;
4-(3-pyridinoxy)benzaldehyde semicarbazone;
4-(4-pyridinoxy)benzaldehyde semicarbazone;
4-(4-chloro-2-pyridinoxy)benzaldehyde semicarbazone;
35 4-(2-pyrimidinoxy)benzaldehyde semicarbazone;
2-phenoxy-5-carboxaldehyde semicarbazone;

2-(4-chlorophenoxy)pyridine-5-carboxaldehyde semicarbazone; and
2-(4-fluorophenoxy)pyridine-5-carboxaldehyde semicarbazone.

7. A method for treating, preventing or ameliorating neuronal loss
5 following global and focal ischemia; treating, preventing or ameliorating
neurodegenerative conditions; treating, preventing or ameliorating
otoneurotoxicity and eye diseases involving glutamate toxicity; treating,
preventing or ameliorating pain; treating, preventing or ameliorating manic
depression; providing local anesthesia; or treating arrhythmias and urinary
10 incontinence, comprising administering to a mammal in need of such
treatment an effective amount of a compound having the Formula I:



I

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

15 Y is oxygen or sulfur;

R₁ is hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl;

20 R₂₁, R₂₂ and R₂₃ are independently hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl, or R₂₁, is defined as above, and R₂₂ and R₂₃ together with the
nitrogen atom to which they are attached form a heterocycle selected from the
group consisting of piperidine, piperazine and morpholine;

25 A₁ and A₂ are independently aryl, heteroaryl, saturated or partially
unsaturated carbocycle or saturated or partially unsaturated heterocycle, any of
which is optionally substituted;

X is one or O, S, NR₂₄, CR₂₅R₂₆, C(O), NR₂₄C(O), C(O)NR₂₄, SO, SO₂
or a covalent bond; where

R₂₄ is hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl; and

30 R₂₅ and R₂₆ are independently hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl.

- 68 -

8. The method according to claim 7, wherein method is for treating, preventing or ameliorating pain and said pain is one of neuropathic pain, surgical pain or chronic pain.

5 9. The method according to claim 7, wherein:

A_1 and A_2 are phenyl moieties, that are each independently optionally substituted by one or two substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, cyano, C_{1-6} alkoxy and C_{6-10} aryloxy;

10 Y is O;

R_1 is hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl or C_{6-10} aryl;

R_{21} , R_{22} and R_{23} are independently hydrogen or C_{1-6} alkyl; and

X is oxygen or sulfur.

15 10. The method of claim 7, wherein:

A_1 is an optionally substituted aryl group selected from the group consisting of phenyl and naphthyl, and A_2 is an optionally substituted heteroaryl or aryl group selected from the group consisting of pyridyl, pyrimidinyl, 1,3,5-triazinyl, furanyl, thiophenyl, naphthyl, quinolyl, 3,4-methylenedioxyphenyl, 3,4-ethylenedioxyphenyl, indanyl, tetrahydronaphthyl and quinoxalinyl.

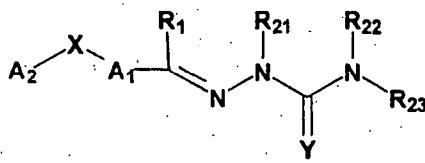
20

11. The method of claim 7, wherein

25

A_1 is an optionally substituted aryl group selected from the group consisting of phenyl or naphthyl, and A_2 is an optionally substituted carbocycle or heterocycle selected from the group consisting of cyclopentyl, cyclohexyl, cycloheptyl, piperidinyl, morpholinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydropyranyl, cyclohexenyl, adamantlyl, *exo*-norbornyl and cyclopentenyl.

12. A compound having the Formula I:



I

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

5 Y is oxygen or sulfur;

R₁ is hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl;

10 R₂₁, R₂₂ and R₂₃ are independently hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl, or R₂₁, is defined as above, and R₂₂ and R₂₃ together with the 15 nitrogen atom to which they are attached form a heterocycle selected from the group consisting of piperidine, piperazine and morpholine;

A₁ and A₂ are independently aryl, heteroaryl, saturated or partially unsaturated carbocycle or saturated or partially unsaturated heterocycle, any of 20 which is optionally substituted;

X is one or O, S, NR₂₄, CR₂₅R₂₆, C(O), NR₂₄C(O), C(O)NR₂₄, SO, SO₂ or a covalent bond; where

R₂₄ is hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl; and

25 R₂₅ and R₂₆ are independently hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl or carboxyalkyl;

provided that:

when X is O or S, and R₂₁, R₂₂ and R₂₃ are hydrogen or alkyl, then A₁ and A₂ are not both phenyl, optionally substituted by one or two non-hydrogen 30 substituents.

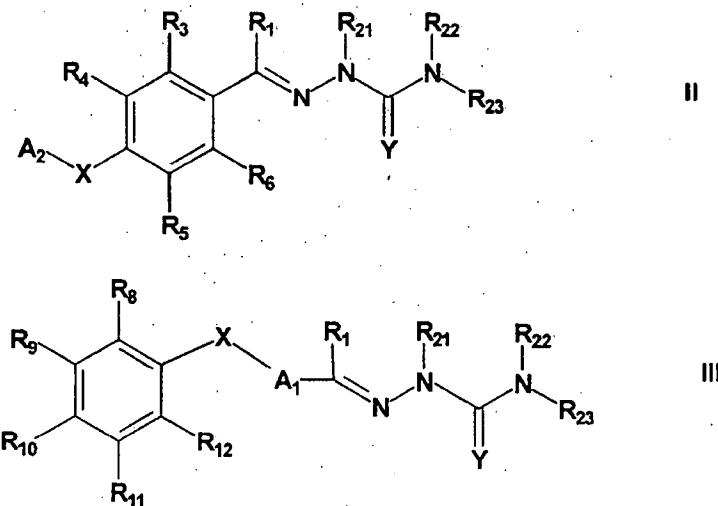
13. A compound according to claim 12, wherein R₂₁, R₂₂ and R₂₃ are independently hydrogen or alkyl.

35

14. A compound according to claim 12, wherein at least one of R₂₁, R₂₂ and R₂₃ is C₁₋₆ alkyl.

15. A compound according to claim 12, wherein R₁ is hydrogen or alkyl.
16. A compound according to claim 12, wherein X is O or S.
- 5 17. A compound according to claim 12, wherein Y is oxygen.
18. A compound according to claim 12, wherein Y is oxygen;
- 10 R₁ is hydrogen, alkyl, haloalkyl, or aryl;
- R₂₁, R₂₂ and R₂₃ are independently hydrogen or alkyl;
- Ar₁ is phenyl or naphthyl, optionally substituted with hydrogen, alkyl, haloalkyl, or halogen;
- 15 Ar₂ is pyridinyl, pyrimidinyl, 1,3,5-triazinyl, 3,4-methylenedioxyphenyl, 3,4-ethylenedioxyphenyl, quinolinyl, quinoxalinyl or naphthyl, optionally substituted with hydrogen, alkyl, haloalkyl, or halogen;
- and
- X is O or S.
- 20 19. A compound according to claim 12, wherein Y is oxygen;
- R₁ is hydrogen, alkyl, haloalkyl, or aryl;
- R₂₁, R₂₂ and R₂₃ are independently hydrogen or alkyl;
- 25 Ar₁ is pyridinyl, pyrimidinyl, 1,3,5-triazinyl, quinolinyl, furanyl, thiophenyl or naphthyl, optionally substituted with hydrogen, alkyl, haloalkyl, or halogen,
- Ar₂ is phenyl, 3,4-methylenedioxyphenyl, 3,4-ethylenedioxyphenyl or naphthyl, optionally substituted with hydrogen, alkyl, haloalkyl, or halogen;
- and
- 30 X is O or S.

20. A compound of claim 12, having Formula II or Formula III:



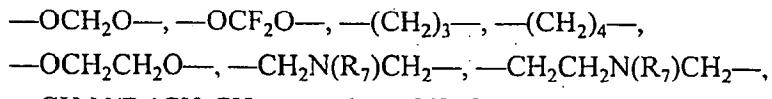
5

or a pharmaceutically acceptable salt or prodrug thereof, wherein

R₁, R₂₁, R₂₂, R₂₃, X, Y, A₁ and A₂ are as defined in claim 12, provided that A₁ and A₂ are other than optionally substituted phenyl; and

10 R₃, R₄, R₅ and R₆ independently are hydrogen, halo, haloalkyl, aryl, cycloalkyl, saturated or partially unsaturated heterocycle, heteroaryl, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, cycloalkylalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxyalkyl, nitro, amino, ureido, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido or alkylthiol; or

15 R₃ and R₄ or R₅ and R₆ form a bridge selected from the group consisting of



20 hydrogen, alkyl or cycloalkyl;

R₈, R₉, R₁₀, R₁₁ and R₁₂ independently are hydrogen, halo, haloalkyl, aryl, cycloalkyl, saturated or partially unsaturated heterocycle, heteroaryl, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, cycloalkylalkyl, heterocycloalkyl,

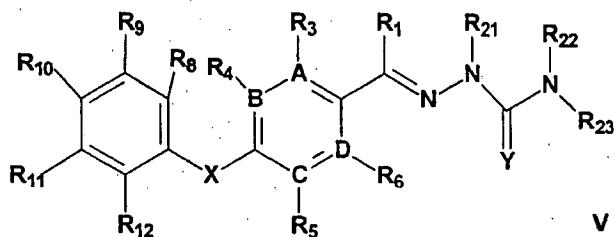
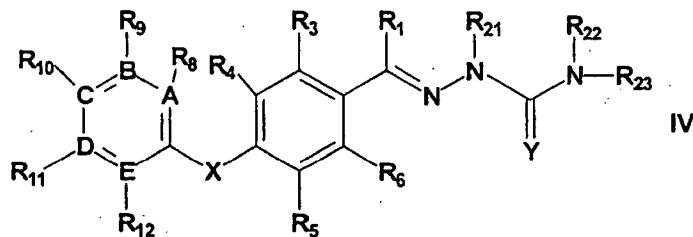
25

hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxyalkyl, nitro, amino, ureido, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido or alkylthiol; or

one of R₈ and R₉, or R₉ and R₁₀, or R₁₀ and R₁₁, or R₁₁ and R₁₂ form a carbocycle or heterocycle selected from the group consisting of —OCH₂O—, —OCF₂O—, —(CH₂)₃—, —(CH₂)₄—, —OCH₂CH₂O—, —CH₂N(R₇)CH₂—, —CH₂CH₂N(R₇)CH₂—, —CH₂N(R₇)CH₂CH₂— and —CH=CH—CH=CH—; where R₇ is hydrogen, alkyl or cycloalkyl.

10

21. A compound of claim 12, having Formula IV or Formula V:



15

or a pharmaceutically acceptable salt or prodrug thereof, wherein

R₁, R₂₁, R₂₂, R₂₃, X, and Y are as defined in claim 12;

20 A, B, C, D and E are independently nitrogen or carbon, provided that no more than three of A, B, C, D and E are nitrogen, and there is no substituent, except for oxygen, present on A, B, C, D or E when said A, B, C, D or E represents nitrogen;

25 R₃, R₄, R₅ and R₆ independently are hydrogen, halo, haloalkyl, aryl, cycloalkyl, saturated or partially unsaturated heterocycle, heteroaryl, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, cycloalkylalkyl, heterocycloalkyl,

hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxyalkyl, nitro, amino, ureido, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido or alkylthiol; or

5 R_3 and R_4 or R_5 and R_6 form a bridge selected from the group consisting of

—OCH₂O—, —OCF₂O—, —(CH₂)₃—, —(CH₂)₄—,
 —OCH₂CH₂O—, —CH₂N(R₇)CH₂—, —CH₂CH₂N(R₇)CH₂—,
 —CH₂N(R₇)CH₂CH₂— and

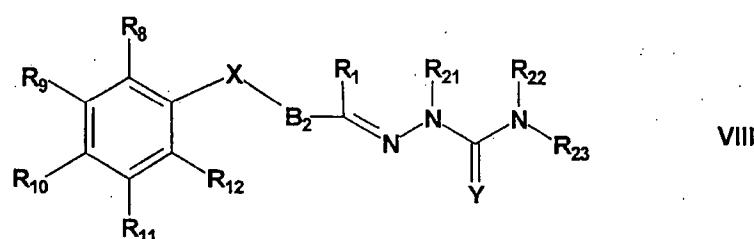
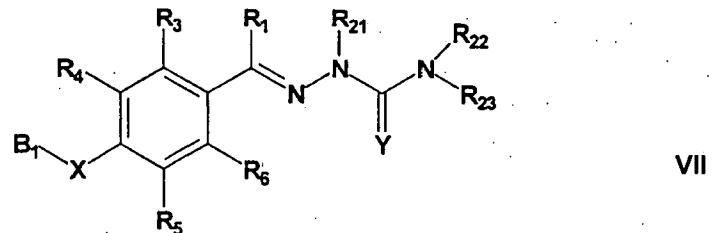
—CH=CH—CH=CH—; where R_7 is hydrogen, alkyl or cycloalkyl;

10 R_8 , R_9 , R_{10} , R_{11} and R_{12} independently are hydrogen, halo, haloalkyl, aryl, cycloalkyl, saturated or partially unsaturated heterocycle, heteroaryl, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, cycloalkylalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxyalkyl, nitro, amino, ureido, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido or alkylthiol; or

15 one of R_8 and R_9 , or R_9 and R_{10} , or R_{10} and R_{11} , or R_{11} and R_{12} form a carbocycle or heterocycle selected from the group consisting of —OCH₂O—, —OCF₂O—, —(CH₂)₃—, —(CH₂)₄—, —OCH₂CH₂O—, —CH₂N(R₇)CH₂—,
 20 —CH₂CH₂N(R₇)CH₂—, —CH₂N(R₇)CH₂CH₂— and —CH=CH—CH=CH—; where R_7 is hydrogen, alkyl or cycloalkyl.

22. A compound of claim 12. having the Formula VII or Formula

VIII:



or a pharmaceutically acceptable salt or prodrug thereof, wherein

R₁, R₂₁, R₂₂, R₂₃, Y and X are as defined in claim 12;

B₁ is an optionally substituted, saturated or partially unsaturated carbocycle or optionally substituted, saturated or partially unsaturated heterocycle; and

5 B₂ is an optionally substituted, saturated or partially unsaturated carbocycle or optionally substituted, saturated or partially unsaturated heterocycle;

10 R₃, R₄, R₅ and R₆ independently are hydrogen, halo, haloalkyl, aryl, cycloalkyl, saturated or partially unsaturated heterocycle, heteroaryl, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, cycloalkylalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxyalkyl, nitro, amino, ureido, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido or alkylthiol; or

15 R₃ and R₄ or R₅ and R₆ form a bridge selected from the group consisting of

—OCH₂O—, —OCF₂O—, —(CH₂)₃—, —(CH₂)₄—,

—OCH₂CH₂O—, —CH₂N(R₇)CH₂—, —CH₂CH₂N(R₇)CH₂—,

20 —CH₂N(R₇)CH₂CH₂— and

—CH=CH—CH=CH—; where R₇ is hydrogen, alkyl or cycloalkyl;

25 R₈, R₉, R₁₀, R₁₁ and R₁₂ independently are hydrogen, halo, haloalkyl, aryl, cycloalkyl, saturated or partially unsaturated heterocycle, heteroaryl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, cycloalkylalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxyalkyl, nitro, amino, ureido, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido or alkylthiol; or

30 one of R₈ and R₉, or R₉ and R₁₀, or R₁₀ and R₁₁, or R₁₁ and R₁₂ form a carbocycle or heterocycle selected from the group consisting of —OCH₂O—, —OCF₂O—, —(CH₂)₃—, —(CH₂)₄—, —OCH₂CH₂O—, —CH₂N(R₇)CH₂—, —CH₂CH₂N(R₇)CH₂—, —CH₂N(R₇)CH₂CH₂— and —CH=CH—CH=CH—; where R₇ is hydrogen, alkyl or cycloalkyl.

23. A compound according to claim 22, wherein B₁ is cyclopentyl, cyclohexyl, cycloheptyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl or piperidinyl.

5 24. A compound according to claim 22, wherein B₂ is cyclopentyl, cyclohexyl, cycloheptyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl or piperidinyl.

10 25. A compound according to claim 12, wherein said compound is
4-(3,4-methylenedioxyphenoxy)benzaldehyde semicarbazone;
4-cycloheptyloxybenzaldehyde semicarbazone; and
4-(5-indanyloxy)benzaldehyde semicarbazone
4-cyclohexyloxybenzaldehyde semicarbazone;
4-(tetrahydropyranyloxy)benzaldehyde semicarbazone;
15 4-(1-methyl-4-piperidinoxy)benzaldehyde semicarbazone;
4-(diphenylmethoxy)benzaldehyde semicarbazone;
4-(4-fluorophenoxy)benzaldehyde 2'-methylsemicarbazone;
4-(4-trifluoromethylphenoxy)benzaldehyde 2'-methylsemicarbazone;
4-(diphenylmethoxy)benzaldehyde 2'-methylsemicarbazone;
20 4-benzylbenzaldehyde 2'-methylsemicarbazone;
4-(5-indanyloxy)benzaldehyde 2'-methylsemicarbazone;
4-(3,4-methylenedioxyphenoxy)benzaldehyde 2'-methylsemicarbazone;
3-fluoro-4-(3,4-methylenedioxyphenoxy)benzaldehyde
2'-methylsemicarbazone;
25 4-(4-nitrophenoxy)benzaldehyde 2'-methylsemicarbazone;
4-(4-fluorophenoxy)-3-fluorobenzaldehyde 2'-methylsemicarbazone; and
4-(4-fluorophenoxy)benzaldehyde 4'-methylsemicarbazone.

30 26. A compound according to claim 12, wherein said compound is
selected from the group consisting of:
4-(2-pyridinoxy)benzaldehyde semicarbazone;
4-(3-pyridinoxy)benzaldehyde semicarbazone;
4-(4-pyridinoxy)benzaldehyde semicarbazone;
4-(4-chloro-2-pyridinoxy)benzaldehyde semicarbazone;

2-phenoxy pyridine-5-carboxaldehyde semicarbazone;
2-(4-chlorophenoxy)pyridine-5-carboxaldehyde semicarbazone; and
2-(4-fluorophenoxy)pyridine-3-carboxaldehyde semicarbazone.

5 27. A pharmaceutical composition, comprising the compound of
any one of claims 12-26, and a pharmaceutically acceptable carrier or diluent.

1/1

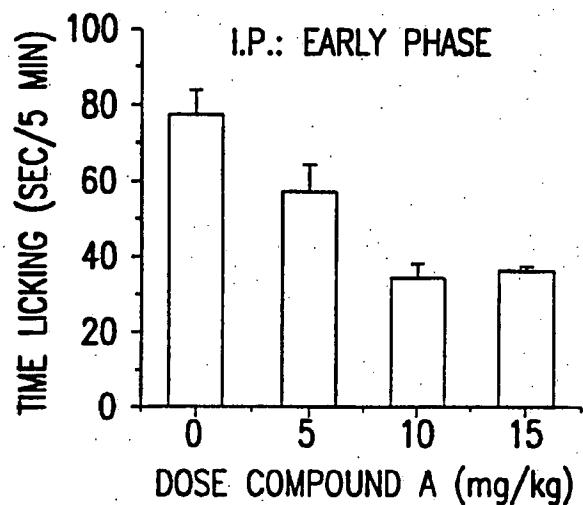


FIG. 1A

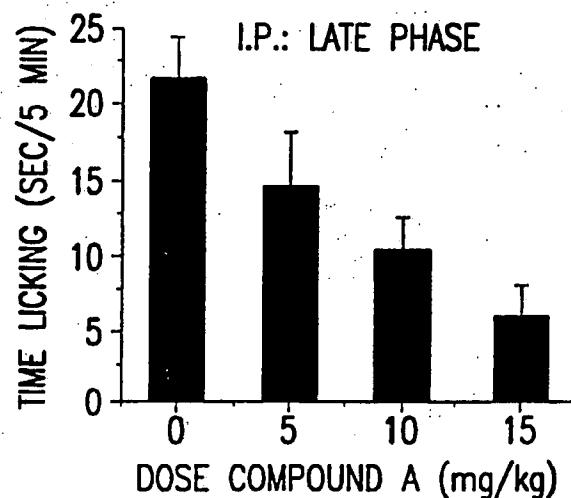


FIG. 1B

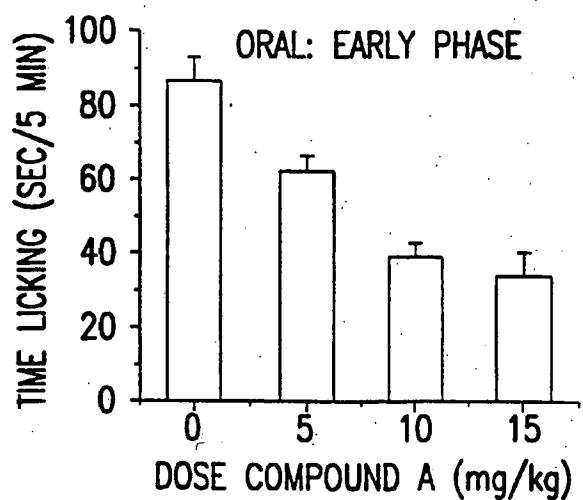


FIG. 1C

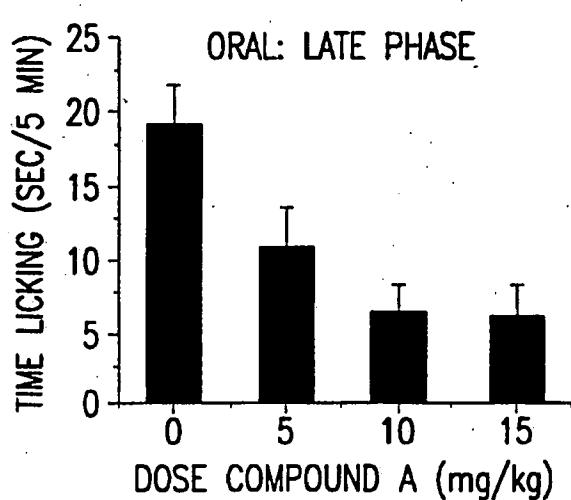


FIG. 1D

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/08004

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.

US CL :514/256, 311, 315, 351, 451 ; 544/242; 546/152, 184, 329; 549/356

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/256, 311, 315, 351, 451; 544/242; 546/152, 184, 329; 549/356

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS COMPUTER SEARCH 1966-TO DATE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96/40628 A1 (THE UNIVERSITY OF SASKATCHEWAN) 19 December 1996; see entire document.	1-27
X	US 5,554,630 A (TEUBER et al) 10 September 1996, columns 23-24.	1, 2, 7, 8, 12, 13, 15, 17 and 27
Y		1, 2, 7, 8, 12, 13, 15, 17 and 27
X	US 5,102,869 A (SHIOKAWA et al) 07 April 1992, see columns 23 and 38.	7, 8, 12-15, 17 and 27
Y		7, 8, 12-15, 17 and 27

Further documents are listed in the continuation of Box C.

See patent family annex.

Special categories of cited documents:	
"A"	document defining the general state of the art which is not considered to be of particular relevance
"E"	earlier document published on or after the international filing date
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O"	document referring to an oral disclosure, use, exhibition or other means
"P"	document published prior to the international filing date but later than the priority date claimed
"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"Z"	document member of the same patent family

Date of the actual completion of the international search

24 SEPTEMBER 1997

Date of mailing of the international search report

08 SEP 1998

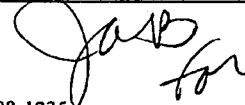
Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer:

ZINNA N. DAVIS

Telephone No. (703) 308-1235



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/08004

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (6): C07D 211/06, 213/02, 215/02, 239/02, 309/02; A61K 31/35, 31/44, 31/445, 31/47, 31/505